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SEROUS HEPATOSIS: A PATHOGENESIS OF HEPATIC FIBROSIS IN JAMAICAN CHILDREN

PRELIMINARY REPORT*

BY

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[WITH SPECIAL PLATE]

The object of this communication is to report upon a disease of the liver found in Jamaican children ; because of its clinico-pathological features we have proposed the term " serous hepatosis " (Hill, 1951 ; Hill *et al.*, 1951).

In all, 150 cases have been investigated. On clinical analysis it is apparent that they can be classified as conforming to certain different types which are, however, different phases of the same disease with the same underlying pathology. Histologically, this condition resembles that described by Roessle (1930) as " serous hepatitis," or that described by Keschner and Klemperer (1936) as " hepatic oedema."

Three methods of approach were used in the study of these Jamaican children. First, a dietary survey was made ; secondly, all children were subjected to a complete examination in which were included certain biochemical tests for liver function ; and, thirdly, needle-biopsy examination was carried out on approximately 50% of cases, from some of which serial biopsies were taken.

Dietary Survey

This has been previously described by Rhodes (1951). The common background of all these children was a poor dietary history starting in early infancy. Most of them were of good average weight when born, and they were breast-fed for a period varying from four to nine months. In Jamaica, however, complete breast-feeding is stopped early and complementary feeding adopted. This means that the baby receives breast milk about twice during the night, and during the day is fed on cereals such as cornmeal, or rolled oats with or without a little condensed milk.

From the neonatal period, except in a few cases, the babies are given " bush tea," which is an infusion of leaves, flowers, or seeds of various plants. When the babies are weaned they are put on a cornmeal diet, although rolled oats and Robinson's patent barley are also used. The diet is monotonous in the extreme, and one of these highly refined cereals is given meal after meal for months and years on end.

For economic reasons, and also because of its poor keeping qualities in the Tropics, cows' milk is seldom used, and little, if any, meat, fish, and eggs is eaten. Often the children are given diluted condensed milk, one to two tins a week being shared by the whole family. Children 4 to 5 years and older live on root vegetables such as yams and sweet potatoes and, in addition, cornmeal and rice.

The dietary history as presented above implies a very low protein intake, particularly low in animal or so-called first-class protein, but an adequate calorie intake. Only a few cases of this series (7%) had a very low calorie intake in addition to a low protein consumption, and these, as shown later, presented a modified clinico-pathological picture.

Clinical Findings

The children were between the ages of 4 months and 16 years, the majority being from 1 to 3 years old. Nearly all were from poor homes, and the remainder came from lower middle-class homes in which the standard of intelligence or the knowledge of what comprises a nutritious diet is low ; possibly associated with this is the fact that the familial incidence of the disease is high. The children are predominantly of African extraction, with European, East Indian, and Chinese racial admixtures.

On examination about one-third of the cases were in the *acute* phase of the disease. About a half of these cases gave a recent history of acute illness such as tonsillitis, whooping-cough, and pneumonia before the onset of gross abdominal enlargement due to ascites and hepatomegaly. The acute illness usually preceded, or sometimes was concurrent with, the liver enlargement. These children were usually normal in physique, and in two or three weeks they recovered from the acute hepatic involvement, though often they had a residual asymptomatic enlargement of the liver. Liver-function tests showed an absolute rise in serum globulin with a reversed albumin/globulin ratio and a lowered serum cholinesterase. Recovery from the acute liver enlargement occurred whether or not treatment was given for this condition.

The other half of the patients in the acute phase had no previous history of infection so far as could be elicited. They had ascites and an enlarged firm liver. The liver-function tests generally showed a lowered serum albumin, often with a low total protein and also a low serum cholinesterase. On a high-protein diet it was two to three months

*Submitted in December, 1951.

†In receipt of research grants from the Josiah Macy Jr. Foundation.

before they improved from the acute phase. A few apparently recovered completely, but frequently they tended to lapse into the subacute or the chronic phase.

All the children in the acute phase were very ill and fretful. The liver was hard with a smooth outline and a sharp lower edge, and both the left and the right lobes were enlarged. Sometimes the liver was bulging and tender on pressure as if under tension. Occasionally the enlargement was great, up to 12 cm. below the costal margin; a varying degree of ascites was present, and on first paracentesis the protein content was sometimes as high as 2.1 to 2.8%. On subsequent tapping the protein content decreased.

Signs of vitamin deficiency were rare. The appearance of these children was in striking contrast to the usual picture of subnutrition found in the Tropics (Waterlow, 1951).

About one-third of the series were found to be in the subacute stage when first examined. They usually looked well developed, with rounded contours and adequate subcutaneous fat, although on closer examination some had flabby muscles, some were stunted, and many were underweight. The liver was often slightly or moderately enlarged and there was little or no ascites. Liver-function tests generally showed lowered serum albumin and serum cholinesterase. The results of the flocculation tests were not significant. Jaundice was absent, although not infrequently the total serum bilirubin was slightly raised. Many of these subacute cases were, however, asymptomatic, and were found only on routine examination at schools or on investigation of brothers and sisters of affected children. There was no complaint, and the child was usually happy and looked well, had no ascites, but had an enlarged liver. In a recent survey (not connected with this study) of 116 children from two villages, 55% were found to have symptomless liver enlargement.

About one-third of the series were seen in the chronic phase of the disease. They were usually older children with a long medical history. The picture was one of hepatic fibrosis with a large, nodular, or contracted liver, with sometimes an enlarged spleen and clubbing of the fingers and toes, an established collateral circulation, and occasionally jaundice. These children were retarded and of poor nutrition. Two cases have been followed from the subacute stage to the chronic stage over a period of a year.

Eleven cases in the whole series were starved babies with generalized oedema, loss of subcutaneous fat, and signs of vitamin deficiency such as angular stomatitis, depigmentation of the hair, and various dermatoses which have been described in the literature many times as part of the syndrome of kwashiorkor or fatty liver disease. These babies were on a low-calorie diet, and the usual history was loss of appetite for one to three months and subsequent feeding on sweetened "bush tea" as a home remedy. Oedema was always present and not necessarily associated with ascites, the oedema being presumably a starvation phenomenon. These cases had a high mortality, whilst in all the other cases the mortality was low, with a high and prolonged morbidity.

No case in the series showed severe anaemia, but some degree of slight or moderate iron-deficiency anaemia was often seen. Bleeding and coagulation times were normal. Sickling trait was found in 7% of the cases and 11% showed infection with *Ancylostoma duodenale, Trichuris trichiura,* or *Ascaris lumbricoides.* Malaria parasites in the blood were demonstrated in three cases.

Histology

Liver-needle biopsies were performed on 75 out of the 150 cases studied; in many cases serial biopsies were obtained. Specimens were fixed in various agents from time to time—for example, formalin, corrosive sublimate, alcohol, and Zenker's solution—but for the majority formal-sublimate solution was found to be the most suitable. Up to 80 serial sections of blocks were cut and sections were stained routinely with H. and E., periodic acid Schiff (P.A.S.), picro-Mallory connective-tissue stain, and Foote–Wilder reticulin stain; special stains for amyloid, fibrin, glycogen, haemoglobin, and fat were done when indicated.

In 25% of cases an early exudative or transudative lesion was found; this consisted of out-pouring of serous fluid into the perisinusoidal spaces of Disse and around the centrilobular veins (Special Plate, Figs. 1, 2, and 3). In some cases the lesion occupied almost the whole of the liver biopsy section under examination, but in most cases the lesion was focal and multiple, each lesion involving up to one or two lobules. The unaffected liver tissue seemed to be quite healthy, but the liver-cell columns at the site of the actual lesions appeared to be flattened. Whether or not they were in fact compressed or whether they were atrophied or shrunken it is impossible to say at the present stage of this investigation. The Kupffer cells and other endothelial cells often seemed to be swollen, increased in number, and detached.

Generally in the liver sections the sinusoids were dilated and filled with blood; alternatively, the sinusoids were wide open and empty, but this was thought to be artifact due to draining out of the blood at the time of biopsy. In about 15% of cases there were focal areas of fresh haemorrhage at the sites of recent serous exudation. This haemorrhage was thought to be due to trauma at the time of biopsy of unduly fragile and congested capillaries; no focus of old haemorrhage was found, no iron-containing brown pigment or macrophagic reaction was ever observed to suggest haemorrhage as part of the disease process, and in only one or two cases was the haemorrhagic artifact found in serial biopsy *after* treatment.

In 80% of cases deposition of an eosinophilic coagulum was found in the spaces of Disse (Figs. 3, 4, 5, and 6) and "cuffing" the centrilobular veins. This was associated in about one-third of these cases with oedema of the space of Disse mentioned above, as if the coagulum had been precipitated out of the serous fluid or perhaps the fluid, a sol, had become a gel.

At this stage the study of the chemical nature of the serous fluid has not been established, although we are of the opinion that it is probably initially exudative in character; accordingly the term "exudate" will be used in this context.

Sometimes the serous exudate alternated with the coagulum around the centrilobular veins, giving the lesions a laminated appearance; this was interpreted as indicating repeated attacks of liver disease. Although, however, in about two-thirds of the cases the eosinophilic coagulum was found alone, it was probably secondary to the serous exudation.

The eosinophilic coagulum gave the tinctorial reactions of collagen, and was not digested by trypsin. In appearance it varied from a granular amorphous coagulum to waxy-looking blobs of material; on occasion it had a fibrillary appearance although almost acellular—that is, there were no fibroblasts (Fig. 3). Tinctorially it was not amyloid, paramyloid, or atypical amyloid (Teilum, 1948), or fibrin or haemoglobin; it was not birefringent with Congo-red stain and not metachromatic with toluidine blue.

Reticulin stains (Figs. 7 and 11) revealed a perisinusoidal reticulinosis which showed swollen reticulin fibres in the perisinusoidal spaces (at the site of the coagulum), with condensation and possible proliferation, although this latter may be illusory. In places where the coagulum was abundant it could be seen as laminated yellow-coloured blobs adherent to black swollen reticulin fibres (Fig. 6).

In 50% of cases there was distension of the space of Mall in the portal triads by serous exudation (Fig. 8), and in some of these cases there was evidence of a recent deposition of eosinophilic coagulum within the exudate. Often there appeared to be a dilatation of the perivascular and periductal lymphatics.

The coagulum extended from the space of Mall, surrounding the intralobular and interlobular vessels arising from the vessels of the portal triads (Fig. 9).

In 75% of the cases fibrosis of the eosinophilic coagulum was seen. The youngest patient was aged 4 months. Fibroblasts could be seen invading the coagulum around the centrilobular vein and along the spaces of Disse (Fig. 10). In the former there were bands of perivascular fibrosis extending from lobule to lobule (reversed lobulation); in the latter there was perisinusoidal fibrosis distorting the lobule in all directions, and in some cases a vascular short-circuit was produced from portal triad to centrilobular vein. The fibrosis of the coagulum around the intralobular vessels contributed to the further intralobular distortion, whilst the fibrosis of the interlobular vessels produced the appearance of perilobular cirrhosis (Fig. 11).

Of the cases 30% showed extreme fibrosis with distortion, bile-duct proliferation, and nodular hyperplasia, an appearance generally associated with cirrhosis (Figs. 12 and 13).

In general, liver-cell damage was not observed except in cases with marked fibrosis, although at this stage of the investigation special histochemical stains have not been done. The liver cells were often slightly swollen or hydropic in appearance; generally, but not invariably, this was shown to be due to a high glycogen content. In five cases there was fatty metamorphosis, but in three cases this was associated with recent or old-standing serous exudation or deposition of eosinophilic coagulum. Cellular infiltration of portal triads was slight, and was associated with fibroblastic invasion of the eosinophilic coagulum; it was never observed to such an extent as to suggest infective hepatitis.

In summary, the histological picture appeared to show a train of events beginning with serous exudation followed by the deposition of an eosinophilic coagulum which was subsequently invaded by fibroblasts. Often the three processes were taking place concurrently in the same biopsy block of liver tissue but not necessarily at the same site. The end-result was extensive hepatic fibrosis.

A Pathogenesis of Hepatic Fibrosis: A Theory

The structure of the liver lobule is probably similar to that described by Elias (1949a, 1949b). Fig. A, I is a diagrammatic representation of part of a liver lobule (the centrilobular vein, sinusoid, liver cells, and the portal triad). The sinusoid lies in a lacuna which is lined by the liver cells making up the hepatic laminae (hepatic cell columns). The lacunar space between the hepatic laminae and the sinusoid is the perisinusoidal space of Disse. The hepatic laminae are continuous interconnecting sheets of cells and the lacunal spaces formed by them are also interconnecting to form a labyrinth. The capsule of the portal triad is circumscribed by a potential space—the space of Mall—which connects with the space of Disse. Branches of the portal vessels are the interlobular and intralobular vessels. These all pass through the space of Mall to enter the parenchyma, and in so doing carry with them an enveloping potential space which connects with the space of Mall. Structurally the spaces of Mall and Disse may well be a part of the "lymphatic" drainage of the liver.

The first stage of the pathogenesis of hepatic fibrosis is serous exudation into the space of Disse and around the centrilobular vein (Fig. A, II). Subsequently there is a deposition of eosinophilic coagulum in these areas (Fig. A, III).

Serous exudate and coagulum may be deposited in many areas as a result of repeated attacks; the lesions are focal and circumscribed. At the site of an initial lesion the serous exudation spreads out in all planes as the different lacunae interconnect to make up the hepatic labyrinth. The confinement of the exudation to focal areas may be due to the deposition of eosinophilic coagulum restricting the further spread of serous fluid. Thus any newly formed serous exudate will be prevented from flowing in the direction of the centrilobular vein or laterally into adjoining

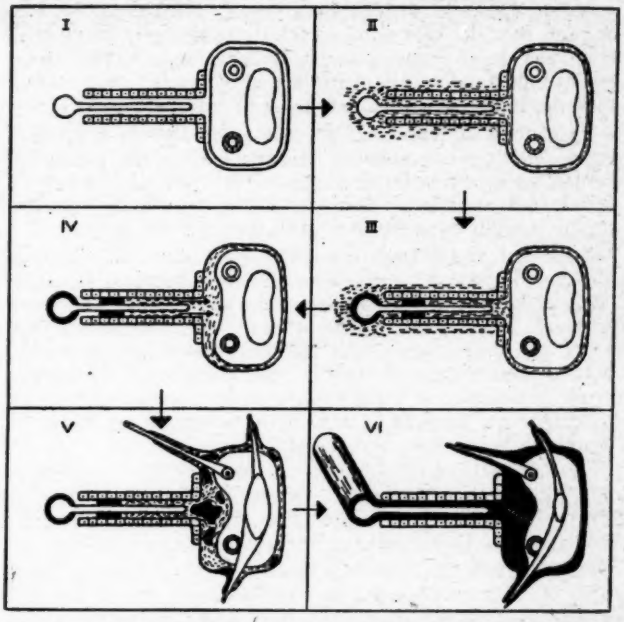

FIG. A.—Diagram showing the various stages of the pathogenesis of hepatic fibrosis. (I) Normal liver lobule with hepatic lacuna between the hepatic laminae; within the lacuna lies the centrilobular vein and sinusoid; the portal triad is shown with peripheral space of Mall which connects with the perisinusoidal space of Disse (lacuna). (II) Serous exudation in perisinusoidal space of Disse. (III) Deposition of coagulum around centrilobular vein and also within the space of Disse. (IV) Distension of space of Mall, following further serous exudation subsequent to the deposition of coagulum. (V) Deposition of coagulum from the serous exudate present in the space of Mall and in the sheaths of the intralobular and interlobular vessels. (VI) Late stage of deposition of coagulum which becomes fibrosed by the invasion of fibroblasts.

lacunae, but rather will be directed into what is probably the natural flow of the liver-tissue fluid, in the direction of the space of Mall in the portal triad. The space of Mall will thus become distended with serous exudate (Fig. A, IV). Subsequently, an eosinophilic coagulum will be deposited around the portal triad and also along the sheath-like spaces enveloping the intralobular and interlobular vessels (Fig. A, V). The sheaths are extensions of the space of Mall.

The next stage is the invasion of the coagulum by fibroblasts; thus there is established a fibrotic cuffing of the centrilobular vein and an intralobular extension of fibrous bands along the space of Disse. At the same time fibroblastic proliferation from the periphery of the portal triads spreads along the interlobular and intralobular vessels (Fig. A, VI).

Subsequent contraction of this fibrous tissue causes lobular distortion and disorganization, which, together with reactive nodular hyperplasia, produce the final picture of diffuse hepatic fibrosis.

Discussion

The series of cases under study illustrate a development of gross hepatic fibrosis beginning as a serous exudation (or oedema), followed by deposition of an eosinophilic coagulum, followed in turn by invasion by fibroblasts.

One outstanding feature of the study was the finding of a serous exudate or transudate and coagulum in the perisinusoidal spaces of Disse and around the centrilobular vein. The source of the serous fluid is, at this moment, undetermined; there are three possibilities: (1) from the sinusoid through the capillary wall; (2) from the liver cells; and (3) from blockage of the normal tissue-fluid drainage—that is, "hepatic lymph" in the spaces of Disse and Mall.

Increase of capillary permeability in the liver due to toxic causes, resulting in serous exudation, is not a new

concept. Roessle (1907, 1930, 1933, 1943) was of the opinion that the escape of serum from damaged capillaries is in the acute stage a serous inflammation. The acute serous inflammation may be followed by a sclerosing lesion; thus the initial stage of cirrhosis is a "serous hepatitis."

This point of view was further elaborated by Eppinger *et al.* (1935), who extended their studies on the escape of serum from capillaries in shock to the general concept of serous inflammation. Eppinger (1949) has lately referred to this condition as "albuminuria into the tissues."

Keschner and Klemperer (1936) have described findings similar to those of Roessle in the perisinusoidal space in 15% of a large series of necropsies; although not agreeing with all Roessle's conclusions, and while preferring the term "hepatic edema" to "serous hepatitis," they concluded that in many cases the hepatic oedema is primarily from toxic causes. They base their conclusion on the association of hepatic oedema with diabetic coma, uraemia, exophthalmic goitre, and thermal burns.

As far back as 1909, Helly had observed the focal flecking of the liver in sepsis, and Keschner and Klemperer (1936) were of the opinion that this was focal hepatic oedema due to generalized toxaemia.

It is interesting to note that Popper (1936b) mentions that Henschen regarded hepatic oedema as a kind of "glaucoma of the liver," and he relieved it in practice by an operation in which he injured the liver surface, thus facilitating the escape of oedematous fluid, with immediate decrease in the size of the liver. Biopsy specimens taken from such a liver with oedema visibly shrank within a few minutes of the operation.

Serous hepatitis has been produced experimentally in dogs by Popper (1936a, 1937), using allyl formate. The lesions produced were similar to those found in serous hepatitis in humans, although there was no certainty in production of the lesions. It would be interesting to note whether the lesions could be produced with 100% certainty if the animals were on low protein diet. Furthermore, the lesions of serous hepatitis have also been produced experimentally by Eppinger and Leuchtenberger (1932) by the intravenous injection of histamine.

Another cause of the escape of serous fluid from the capillaries may be congestion which probably acts by a hydromechanical effect and possibly increasing capillary permeability due to anoxia. Popper (1948) has reported the agonal changes in human livers following acute heart failure, drowning, and asphyxiation, in which there is a dilatation of the perisinusoidal spaces usually associated with accumulation of "albuminoid" material. In a series of cases of instantaneous death no such dilatation of the perisinusoidal spaces was seen. Keschner and Klemperer (1936) record a similar finding in 36% of cases after cardiac failure and describe it as a "mechanical oedema." They were of the opinion that the term "serous hepatitis" for such conditions was inappropriate; after all, if the agonal changes are due only to congestion, the so-called exudate is in fact "transudate."

We have in our laboratory a section from a patient dying from acute right-sided heart failure which shows an eosinophilic coagulum around the centrilobular vein. The fact that these changes can occur agonally in acute right-sided heart failure, whether they be from exudates or transudates, none the less supports the theory that the material in the perisinusoidal spaces occurring in the series of biopsies under study may be derived from vascular sources.

Many of our sections show hepatic congestion—so much so that some of the sinusoids are grossly distended and filled with blood or, alternatively, probably owing to artifact, are wide open and empty. This latter condition was described by Roessle (1930). Further, in 15% of our cases there was fresh haemorrhage, interpreted as being due to capillary fragility, associated with trauma at the time of the biopsy. Our reason for this opinion was that we never at any time saw evidence of old haemorrhage such as iron-containing brown pigment or a macrophagic reaction; further, in only one or two cases, after treatment on a high-protein diet, did we obtain such an artifact, our assumption being that treatment had corrected the abnormal fragility of the capillary wall.

Cardiac failure was not the cause of liver (sinusoidal) congestion in our series of cases. Of the criteria for heart failure laid down by Sherlock (1951), such as crepitations of the lung bases, increased jugular pressure, peripheral oedema, and hepatic tenderness, only the last-mentioned was found clinically; histologically no centrilobular necrosis with graded histological change towards the periphery was found.

Maegraith *et al.* (1949, 1951) have shown that hepatic congestion can be produced in animals by hypersensitivity: this congestion is probably due to constriction *within* the hepatic venous tree. Essex and Thomas (1950) state that they have produced occlusive spasm of the hepatic veins in dogs and cats following intravenous injection of an extract of *Ascaris suis*, hydatid cyst fluid, and histamine.

Another source of the exudate may be from the liver cells themselves. This view has been put forward by Eger (1950), who suggests that there is a release of fluid from the liver cells into the space of Disse, with subsequent retraction of the liver cells. This gains a little support from the present study by the fact that in the foci of exudation the cells sometimes look flattened as though retracted; however, the cells are often swollen with glycogen or are hydropic, changes which are against the opening of the tissue spaces by the mechanical means of retraction.

Further, it is stated by Selye (1950) that the liver parenchymal cells in such conditions of serous inflammation imbibe serum from the tissue spaces with a rise in their sodium chloride, calcium, and water content, and a decrease in their phosphate and potassium content; this imbibition is a possible explanation of the hydropic appearance of liver cells in some of our cases.

The flattened appearance of the cells may be due to atrophy, but, in general, we have observed it only during the acute phase of serous exudation at the site of the exudation; further proof of this theory that the liver cell is the primary site of the liver lesion must await further investigation along the lines of histochemistry and cell and nuclear counts.

Dilatation of the space of Disse may be caused by blockage of the normal tissue-fluid drainage channels of the liver. Popper (1936b) describes the following morphological triad in serous hepatitis: (*a*) dilatation of the perisinusoidal space of Disse; (*b*) oedema of the portal canals; and (*c*) gall-bladder-bed oedema. In cases under study, dilatation of the perivascular and periductal (bile) lymphatics has been noted in association with the distension of the space of Mall. This, of course, as well as suggesting a block in the lymph drainage, may also indicate an increased production of the tissue fluid.

It is interesting to speculate at this stage whether or not the exudate in the perisinusoidal space flows into the perivascular lymphatics of the portal triads and then finally, as a back-pressure effect, into the peritoneal cavity to produce ascites. It is noteworthy that the ascitic fluid on first paracentesis has often a high protein content (2.1 to 2.8 g.%). Gray (1951) has indicated that the source of the ascitic fluid is an excess of hepatic lymph. The hepatic sinusoids are said to be unusually permeable to albumin both in experimental animals (McKee *et al.*, 1949) and in man (Patek *et al.*, 1948).

Experimentally, support for the theory of the drainage of tissue fluid from the perisinusoidal spaces into the lymphatics of the portal triad is given by the work of Koch-Weser (Popper, 1951), who ligated the common bile duct near the liver in rats and produced lesions resembling serous hepatitis. Several authors, including Bollman (1950), have stated that the bile ducts are surrounded by a plexus

of vessels in which the lymphatics are included. Hence ligation of the common duct will exert a block, producing back-pressure distension of the space of Disse.

In the cases under study no evidence of lymph-duct blockage, either inflammatory or mechanical, has been detected, and the evidence points to overproduction of tissue fluid to explain the dilatation of lymph and tissue spaces.

In summary, the evidence available in this preliminary report is that the serous exudation and the coagulum are produced from vascular sources. Whether this is due to an increase in capillary permeability *per se*, or to congestion producing its anoxic and hydromechanical effects, it is impossible to say at this stage of the investigation.

The possibility that toxic factors are a cause of the increase in capillary permeability *per se* has some support. It is significant that the left lobe appears to be enlarged as much as the right. This lobe may drain the blood of the large gut, and if the latter is a source of bacterial or other toxins then the involvement of the left lobe may be thus explained.

It is to be noted that McFarlane and Branday (1945) and Royes (1948), in their articles on liver disease of Jamaican children, suggest toxins in association with low-protein diet as the aetiological agents. The possible toxicity of the various Jamaican "bush teas" is now being investigated. Further, Watson (1951) has pointed out the efficacy of aureomycin and also of enemata on patients suffering from hepatic coma, and he suggests that the action may be to reduce the toxicity by altering the bacterial flora of the gut.

One constant feature is that the serous exudate and the coagulum are never associated with a cellular infiltrate, which is the usual accompaniment of inflammation. However, according to Selye (1950), the emigration of leucocytes can be inhibited by systemic intoxication with bacterial endotoxins and by anaphylactoid, traumatic, and "toxic" shock.

Increased capillary permeability producing hepatic oedema was found by Keschner and Klemperer (1936) in association with asthma; it has also been produced by Eppinger and Leuchtenberger (1932) by the intravenous injection of histamine. These examples would point to the circulation of a toxic histamine-like substance, and may well suggest further experimental work on the lines of hypersensitivity. It is to be noted that two of our cases with primary tuberculous lesions showed acute hepatic enlargement immediately after the tuberculin test, which, as was expected, was positive. Biopsy of the cases showed the histological picture which we have found associated with acute serous hepatosis.

Whatever the source of the exudate, the fact remains that an exudate and/or coagulum are constantly found, and the question may be asked, "What is the coagulum?" The coagulum gives all the tinctorial reactions of collagen and is not digested by trypsin. Is it in fact collagen, or a precursor of collagen? In many cases the coagulum has the waxy appearance of amyloid with H. and E. stain, and in some cases it has a fibrillary appearance although acellular. Reticulin staining shows the reticulin fibres black and swollen, and adherent to them are blobs of laminated material staining yellow. These blobs are in fact the coagulum. Are they blobs of protein from the serous exudate forming on the side of the swollen reticulin fibres or are they swollen reticulin fibres which are blowing up to bursting point at various places along their lengths owing to imbibition of serous fluid?

The fact that the coagulum is acellular does not preclude the possibility of its being collagen or pre-collagen protein material. Porter and Vanamee (1949) have shown in tissue culture, by studies using the electron microscope, that unit fibrils may combine to form protofibrils of collagen without the intermediary of fibroblasts. Further, Porter (1951), in an extension of these studies, has shown that after being shed from the fibroblasts the collagen fibrils increase in size by the accretion of a material from the ground substance. This method of accretion may explain the deposition of protein of serous origin on pre-existing connective-tissue fibres in the liver of the cases under study. The possibility of collagen-fibre formation by precipitation in a protein-rich exudate has also been advanced by Klemperer (1951), and Day and Armstrong (1940) have commented on the curious absence of fibroblastic activity in the genesis of cardiac cirrhosis.

Roessle (1930) explains the sclerosis following serous hepatitis due to the intermediation of endothelial proliferation. The endothelial cells (including the Kupffer cells) increase in number and become detached to form a connective-tissue reticulin—"the endothelialite." In the present study some endothelial swelling and proliferation have been noted, and the few cells seen in the perisinusoidal spaces are often endothelial or Kupffer-cell types.

The coagulum, whatever its derivation, is a precursor of fibrosis. Sections have been studied which show what is interpreted to be the fibroblastic invasion of the coagulum—that is, the coagulum is there first and at a later stage it is invaded by fibroblasts. It is tempting at this stage, therefore, to consider the coagulum as collagen protein or pre-collagen and the process of the laying down of the eosinophilic coagulum as a "collagenosis."

So far, the aetiology of the process of events occurring in the liver has not been determined. One salient fact elucidated has been the woefully deficient protein in the diets; this deficiency was not only in total protein but also in first-class protein of animal origin. It is not known whether the lack of single or multiple amino-acids, or the disproportion of protein to carbohydrates, or perhaps a combination of these factors, contributes to the development of liver disease. At this stage it is pertinent to mention that the cases of serous hepatosis differ both clinically and histologically from those cases of subnutrition with fatty liver disease in the Tropics described as kwashiorkor (Williams, 1933; Trowell, 1949; Davies, 1950; Waterlow, 1951).

It is true that about 7% of the cases conform to the classical description of kwashiorkor. It is of interest that these cases were on a low-calorie as well as a low-protein diet, in contradistinction to the main type of case, which had a low protein but normal calorie intake. Notwithstanding the clinical appearance of starvation and fatty metamorphosis of the liver, evidence of an underlying pathological condition similar to the main group of the cases was found. It is tempting, therefore, to assume that the fatty metamorphosis in these few cases was a side-effect to starvation—that is, deficient calories in the diet.

Mottram (1909) drew attention to the fact that fatty metamorphosis of the liver may be encountered in some cases of starvation, a feature now well recognized in severe deficiency states. Dible (1951) suggests that in such cases the liver cells receive more fat than they are capable of dealing with, and he strongly asserts that there is little evidence that fatty metamorphosis is a precursor of human cirrhosis, as, for example, accepted by Moschcowitz (1948), pointing out that the dietary evidence from experimental work cannot be directly applied to man. Hartz (1949) has described a fatty metamorphosis occurring in children in Curaçao which he claims never goes on to cirrhosis.

Liver-cell damage has been noted (using the usual routine staining methods) only in association with marked hepatic fibrosis. Further study is needed to decide whether or not liver-cell damage is an important feature of the disease under investigation. The results of liver-function tests are, except for a persistent lowered serum albumin and serum cholinesterase, equivocal, and do not conform to any set pattern. None the less, functionally the liver cells would be expected to be defective because the exudate and coagulum in the perisinusoidal spaces (haematoparenchymal barrier) must impair the diffusion of nutrients from the blood stream to the cells. Further, the removal of waste products from the cells to the capillaries will also be

impaired, and therefore local intoxication and malnutrition of the parenchymal elements must follow the initial stage of disturbed capillary permeability. This has been pointed out by Eppinger *et al.* (1935), as well as the fact that excessive amounts of serum proteins in the perisinusoidal spaces may well lead to the invasion of the parenchymal cells by serum proteins and by serum enzymes, resulting in damage to the cell (Böck and Popper, 1937).

The final picture of serous hepatosis is diffuse hepatic fibrosis. This has been arrived at by a slowly progressive fibrosis, intralobular and also perilobular in distribution, which occurs in the coagulum deposited in these positions. A theory has been postulated which attempts to explain the pathogenesis of this fibrosis.

Serous hepatosis, then, may well be one of the causes of polylobular cirrhosis, which Dible (1951) refers to as "cryptogenic."

Summary

A liver disease occurring in Jamaican children has been described; because of its clinico-pathological aspects it has been named "serous hepatosis." To date the only aetiological factor which has been ascertained is a low dietary protein intake. It is suggested that toxic factors may also play a part.

Clinically, the condition occurs in children, usually between the ages of 1 and 3 years, who have an enlarged firm liver and ascites; ultimately the appearance may be one of classical hepatic cirrhosis.

Histologically, the disease is a progressive one, passing from an initial exudation or oedema to the deposition of an eosinophilic coagulum which is finally invaded by fibroblasts.

The condition is similar to that described by Roessle (1930) as "serous hepatitis."

A theory of the pathogenesis of liver fibrosis has been postulated.

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TREATMENT AND PROGNOSIS OF ACUTE PERFORATED PEPTIC ULCER

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During the last decade there has been a striking fall in the fatality of acute perforated peptic ulcer. Whereas before 1942 the operation mortality was commonly 20%, the figure to-day is not more than a quarter of that level. This fall can mainly be attributed to improvements in anaesthesia with the introduction of muscle relaxants and to the use of antibiotics. Deaths from peritonitis in the first week have almost ceased to occur, and fatal cases are now mainly due to concomitant bleeding, intestinal obstruction, and associated diseases. This was demonstrated in the series reported by Avery Jones, Parsons, and White (1950). With the reduction in fatality, interest has been aroused in new methods of management.

Three methods are currently recommended—medical management with gastric aspiration, simple surgical closure, and immediate partial gastrectomy. The choice, in the individual case, must depend on the facilities available, but it will be influenced by knowledge of the immediate and late prognosis in similar cases treated by each method, and it will not necessarily be the same for all patients. It is difficult, on the existing evidence, to assess the relative merits of the three methods, partly because the fatality associated with each method has been rapidly decreasing, and partly because insufficient attention has been paid to the end-results, after the patients have left hospital.

The series reported by Avery Jones, Parsons, and White included 490 patients treated at the Central Middlesex Hospital during 1938–48, the great majority of them by simple surgical closure of the perforation. Since 1948 patients at the hospital have, in the main, continued to be treated by the same method, and the results have been analysed for a further period of three years to see, first, whether the fatality has continued

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to fall; secondly, whether a figure can be obtained for the fatality from surgical closure for comparison with the results obtained by other methods; and, thirdly, whether indications can be defined for the choice of patient to be treated medically with gastric aspiration or by immediate partial gastrectomy.

Immediate Prognosis

Table I shows the number of patients, operated and unoperated, with the corresponding number of deaths each year from 1938 to 1951. Patients diagnosed as having "leaking ulcers" are not included. The table shows that there has been no recognizable change in fatality since the beginning of 1947, when the standard treatment described by Avery Jones, Parsons, and White was adopted. In the five years 1947–51 the total fatality in 340 cases, including those undiagnosed till after death, was 7.9%. The operative mortality in 320 cases was 3.1%. Nineteen patients were treated by immediate partial gastrectomy without a death and 301 were treated by surgical closure of the perforation with 10 deaths, giving a mortality of 3.3%.

TABLE I.—*Prevalence and Fatality of Perforated Peptic Ulcers, 1938–51; Operated and Unoperated Cases*

Year:	1938	1939	1940	1941	1942	1943	1944	1945	1946	1938–46	1947	1948	1949	1950	1951	1947–51	1938–51
Patients operated on	39	35	32	38	33	44	41	41	46	349	52	54	64	67	83	320	669
No. of deaths	12	8	7	7	11	3	4	5	3	60	3	1	0	3	3	10	70
Patients not operated on*	0	1	0	2	2	3	7	4	7	26	6	3	5	2	4	20	46
No. of deaths	0	1	0	2	2	3	6	4	7	25	5	2	5	2	3	17	42
Total perforations	39	36	32	40	35	47	48	45	53	375	58	57	69	69	87	340	715
No. of deaths	12	9	7	9	13	6	10	9	10	85	8	3	5	5	6	27	112

* Necropsy examinations were performed more frequently in the later years, and it is possible that some fatal perforations were missed in the period 1938–42.

Unoperated Cases

Forty-six patients were not operated on. Medical treatment did not include the use of gastric aspiration until after 1946; since then it has been used routinely in cases diagnosed in life. The reasons for which operation was withheld and the results of treatment are given in Table II.

TABLE II

	1938–46		1947–51	
	Cases	Deaths	Cases	Deaths
Perforation undiagnosed	12	12	5	5
Patient too ill	13	12	9	9
Medical treatment preferred	1	1	5	3
Operation refused	—	—	1	0

One diagnostic error was failure to recognize perforation in patients who had recently had a severe haematemesis or melaena; the diagnosis in this group was sometimes particularly difficult because of the presence of peripheral circulatory failure and the lack of abdominal tenderness and rigidity. The double complication was unrecognized in six instances, all during the period 1938–46. Other patients were thought to have coronary thrombosis, mesenteric thrombosis, or carcinomatosis; others came into hospital unconscious and no diagnosis was made.

The majority of the patients in whom perforation was diagnosed and who were not operated on had peripheral circulatory failure and could not be resuscitated sufficiently for operation; they cannot be used for assessing the results of medical treatment. It is, however, of interest that the sole patient who recovered without operation prior to 1947 was shown radiographically to have a gastric ulcer after recovery from the perforation and died five years later from a slowly growing carcinoma originating in the same part of the stomach.

Surgical Closure of the Perforation

The crude fatality rate is of limited value for comparative purposes, since fatality also depends on a number of factors other than treatment, and these are not always constant. Factors usually considered to influence the fatality of perforated ulcers are the sex and age of the patient, the site of the ulcer, and the duration of the delay between onset and institution of treatment. From the experience of the results in the whole series of surgically treated cases, it can be shown that differences in the fatality rate in men and women can be adequately explained by the greater proportion of women among patients with gastric perforations and among those in whom operation is delayed more than 12 hours. On the other hand, the age of the patient, the site of the ulcer, and the duration of delay all affected the fatality independently of one another. The results are shown in Table III. The expected numbers of deaths have been calculated by allowing for the effects of all the other factors under consideration. For example, to obtain the expected numbers of deaths in men and in women, the numbers of men and of women with perforations in each age, site, and duration of delay subgroup were multiplied by the fatality rate for persons in that subgroup and the resulting products for each subgroup were added.

TABLE III.—*Fatality of Perforated Gastric and Duodenal Ulcers Treated Surgically, 1938–51. Subdivided by Sex and Age of Patient, Site of Ulcer, and Duration of Delay Before Treatment**

Factor Affecting Fatality	No. of Cases	No. of Deaths Obs.	No. of Deaths Exp.	Factor Affecting Fatality	No. of Cases	No. of Deaths Obs.	No. of Deaths Exp.
Sex:				Site:			
Male	598	62	62·5	Stomach	122	27	16·4
Female	53	7	6·5	Duodenum	529	42	52·6
				Duration of delay:			
Age:				Less than 6 hr.	370	25	33·6
Under 35	146	7	13·1	6–11 hr.	197	15	23·1
35–44	155	5	13·6	12–17 ,,	43	11	7·1
45–54	161	19	15·6	18 hr. and over	41	18	5·2
55–64	118	24	16·4				
65 and over	71	14	10·3				

* Eight cases with one death have been omitted because the case records were incomplete, and 10 cases of perforated jejunal ulcer with no deaths have been excluded as being too few for separate analysis.

The excess mortality from perforated gastric ulcers is striking; it occurred in each age group, but to a significant extent only when the duration of delay was *less* than six hours (Table IV). The reason for the excess mortality

TABLE IV.—*Duration of Delay*

Hours:	Less than 6	6–11	12–17	18+
Duodenal perforations:				
Observed deaths	11·	9	7	15
Expected ,,	20·5	10·9	7·0	14·2
Gastric perforations:				
Observed deaths	14·	6	4	3
Expected ,,	4·5	4·1	4·0	3·8

from gastric ulcers in the group of patients who reach hospital without much delay may perhaps be that very large perforations occur more readily in gastric ulcers and that these result in immediate massive soiling of the peritoneum and also bring the patient rapidly to hospital with urgent symptoms.

Whether the same factors continue to influence the fatality rate now that it has been greatly reduced cannot yet be determined; the presumption must be that they do. The results for the period 1947–51 are therefore shown in Table V, subdivided by age of the patient, site of the ulcer,

TABLE V.—*Fatality of Perforated Gastric and Duodenal Ulcers Treated by Surgical Closure of the Perforation, 1947–51; Subdivided by Age of the Patient, Site of Ulcer, and Duration of Delay Before Treatment**

Age of Patient	Duration of Delay in Hours					All Durations
	Less than 6	6–11	12–17	18+	Not Known	
Duodenal Ulcers						
Under 35 ..	45	20	1	3 (1)†	0	69 (1)
35–44	38 (1)	22	3	2	3	68 (1)
45–54	39 (1)	23	3	1	0	66 (1)
55–64	12	12	2 (1)	1	0	27 (1)
65 and over ..	13 (1)	7	5	2 (1)	1 (1)	28 (3)
All ages ..	147 (3)	84	14 (1)	9 (2)	4 (1)	258 (7)
Gastric Ulcers						
Under 35 ..	3	2	1	0	0	6
35–44	5	1	0	0	0	6
45–54	3	3 (1)	1	1	0	8 (1)
55–64	3	6	2 (1)	2	0	13 (1)
65 and over ..	2 (1)	2	2	0	1	7 (1)
All ages ..	16 (1)	14 (1)	6 (1)	3	1	40 (3)

* In the same period three patients with perforated jejunal ulcers were also treated by surgical closure of the perforation; all survived.
† The numbers of fatal cases are shown in parentheses.

TABLE VI

Cause of Death	No.	Sex	Age	
Death during induction of anaesthetic	1	M	68	D.U.
Post-operative shock (i.e., death within 48 hours of operation and including early death due to peritonitis) ..	2	M	64	D.U.
		M	69	D.U.
Chest infections	2	M	59	G.U.
		M	70	G.U.
Haemorrhage from the ulcer (3rd to 22nd day)	3	M	47	D.U.
		M	47	G.U.
		M	69	D.U.
Intestinal obstruction (13th day) ..	1	M	43	D.U.
Pulmonary embolus (22nd day; following further laparotomy) ..	1	M	24	D.U.

and duration of delay, so that any part played by these factors can be allowed for in assessing the significance of the overall fatality rate. The causes of death in the ten fatal cases are given in Table VI. More radical treatment of the ulcer at the time of perforation might perhaps have reduced the fatality by eliminating the possibility of subsequent haemorrhage.

Partial Gastrectomy

Since the beginning of 1948 selected patients have been treated by partial gastrectomy. Up to the end of 1951, 19 patients had been so treated without a fatality; in the first six months of 1952 the number has been increased to 30. The total is too small for detailed comparison of the results with those obtained by surgical closure, but it would at least appear that the immediate prognosis is good enough to justify continuing with the treatment. The patients were to some extent selected to exclude bad risks—for example, no patient was aged more than 65—but, on the other hand, five patients were specifically treated by this method because of the dangerous association of haemorrhage with the perforation.

The operations have been performed by a number of surgeons, and the indications for the choice of the method of treatment have been varied; they are discussed in detail later.

Association of Haemorrhage and Perforation

Thirty-four patients in the series presented with a perforated ulcer within a fortnight of having had a haematemesis or a melaena; most commonly the haemorrhage had occurred within the preceding 24 hours. In six instances the perforation was unrecognized till after death. The results of treatment in the 28 diagnosed cases are shown in Table VII.

TABLE VII

	1938–46		1947–51	
	Cases	Deaths	Cases	Deaths
Medical treatment ..	—	—	2	2
Surgical closure	13	6	8*	1
Partial gastrectomy ..	—	—	5	0

* Including one case of perforated jejunal ulcer.

Until 1947 the association of the two conditions gave rise to a very high fatality rate. Since then the results would appear to have been better, irrespective of the type of surgical treatment employed. The numbers are, however, too small to justify a confident conclusion. The two patients treated medically were aged 71 and 86, and medical treatment was considered preferable because of their age; both died. As a result of this experience, surgery is now preferred if it is at all feasible, and two further cases occurring in men aged 71 have been treated successfully by surgical closure of the perforation. The oldest patient treated by partial gastrectomy was 63.

In 40 patients haemorrhage occurred after treatment of the perforation had been instituted. Five of these were patients included above who had also bled with or shortly before their perforation and in whom the perforation had been treated by surgical closure; four died. In another fatal case the haemorrhage appeared after a perforation which was not operated on. In the remaining 34 patients haemorrhage appeared after surgical closure of the perforation; the results of treatment are given in Table VIII.

TABLE VIII

Treatment of the Haemorrhage	1938–46		1947–51	
	Cases	Deaths	Cases	Deaths
Medical	24*	10	6	2
Emergency partial gastrectomy	—	—	4†	0

* Including one case of perforated jejunal ulcer.
† Including one patient, aged 70, operated on three days after closure of the perforation.

In view of the evident tendency for bleeding to recur it would appear that immediate partial gastrectomy is the preferable treatment for perforations associated with or following shortly after haemorrhage; it is likely that it will also give better results for haemorrhage following perforation.

Late Prognosis

The late prognosis has not been studied in all the patients because of the extensive follow-up investigation carried out by Illingworth, Scott, and Jamieson (1946). Their report, however, did not distinguish between gastric and duodenal perforations, and a limited study has therefore been made to determine whether the late prognosis is materially affected by the site of the perforation.

During the period 1938–48, 74 patients diagnosed as having perforated gastric ulcers were treated by surgical closure of the perforation and survived the immediate post-operative period. Their subsequent course was compared with that of the same number of patients who survived the same operation for a perforated duodenal ulcer. The duodenal patients were of the same sex, of the same 10-year age group, and had perforated as closely as possible before or after the corresponding gastric ulcer patients. All were

followed up to the anniversary of their perforations in 1950 or until their ulcers were treated by partial gastrectomy—whichever was the earlier. The period available for follow-up is at least two years in all cases, and extends up to 12 years in some; the result of the method of selection, however, is that the average periods were similar in the two groups, being 6.3 years (S.D. 3.3 years) in the gastric ulcer patients and 6.2 years (S.D. 3.3 years) in the duodenal ulcer patients. Both groups contained the same proportion of men (63/74), and the average ages of the groups were 49.9 years (S.D. 14.8 years) and 49.4 years (S.D. 14.2 years).

The late results of the operation are shown in Table IX. It is seen that the main difference between the prognosis of gastric and that of duodenal patients is that those with

TABLE IX.—*Late Results Following Surgical Closure for Perforated Gastric and Duodenal Ulcer*

Result	After 2 Years		At Follow-up (i.e., after 2–12 Years)	
	G.U.	D.U.	G.U.	D.U.
Untraced	4	4	6	4
Dead, cause attributed to:				
Peptic ulcer	2	1	3	4
Carcinoma of stomach	6	0	8	0
Other disease	2	3	6*	8†
Total dead	10	4	17	12
Living:				
A. Readmitted for gastric symptoms				
Partial gastrectomy	9	6	15	11
Other gastric operations	3	3	3	7
Medical treatment	8	7	6	6
B. Not readmitted for gastric symptoms				
Recurrence of ulcer pain	13	18	11	14
Occasional mild pain or dyspepsia	7	6	5	5
Sympton-free	19	22	11	15
C. State not known	1	4	—	—
Total living	60	66	51	58
Total cases	74	74	74	74

* Certified causes were cancer of the lung (2), heart failure, bronchopneumonia, hypertrophy of the prostate, and enemy action.
† Certified causes were pulmonary tuberculosis, cancer of the larynx (an operation for pyloric stenosis had been performed a few months earlier), myocardial degeneration (2), pneumonia, asthma, intestinal obstruction, and chronic nephritis.

perforated "gastric ulcers" have an appreciable risk of dying of carcinoma of the stomach (11% against 0%). The eight cases shown in Table IX as dying of carcinoma of the stomach include seven reported previously (Doll, 1950). The additional case was traced in the course of the present study (Case 1).

Case 1.—A man aged 61 was admitted on July 2, 1946, with a four-months history of abdominal pain, which had been treated elsewhere as being due to a gastric ulcer; for four hours he had had severe epigastric pain of sudden onset. At operation a perforated gastric ulcer 2 in. (5 cm.) in diameter was found low down on the anterior wall of the lesser curvature. The perforation was closed by an omental graft because, "owing to the size of the ulcer and surrounding oedema, stitches could not be inserted." Recovery was uneventful. Gastroscopy on July 24 revealed antral spasm, which prevented a full view being obtained. He was discharged on July 31. Two months later he complained of daily vomiting, and a barium meal showed a large stomach with a 24-hour residue and a deformed duodenal cap. He was readmitted and a partial gastrectomy was performed on September 27. The pylorus was found to be much distorted and thickened from the presence of an "ulcer" on the anterior wall. The stomach was not examined microscopically. He kept well for three years, when he began to complain of lassitude and, at the beginning of March, 1950, of painless jaundice. He was readmitted on April 24, 1950, and died on July 5. At necropsy the remnant of the stomach was healthy. The liver was found to be enlarged and the common bile duct was obstructed by a carcinomatous mass in the porta hepatis. No other growth was found anywhere else in the body. It is presumed that the original antral ulcer was malignant.

Another patient (Case 2) might also be classified as having had a carcinoma of the stomach at the time of perforation, but he has been classified in Table IX among those patients dying of some disease other than peptic ulcer or carcinoma of the stomach, as the carcinoma is presumed to have been a secondary.

Case 2.—A man aged 60 was admitted on May 22, 1948, with a history of abdominal pains for ten months and severe pain of sudden onset for eight hours. At operation a perforated gastric ulcer was found on the middle third of the greater curvature posteriorly; closure was obtained by oversewing with omentum. He made an uneventful recovery. A barium meal on June 8 showed an irregular ulcer crater in the middle third of the lesser curvature, with the greater curvature drawn in opposite it. Gastroscopy on June 10 showed a mid-gastric contraction ring with some thickening of the mucosa posteriorly; no ulcer was seen and the stomach beyond the constriction was normal. A repeat gastroscopy on July 8 showed no change. He was discharged on July 8 and kept well apart from a cough, which developed at the end of September. In April, 1949, he was admitted to Hillingdon Hospital complaining of pain in the right arm, and on June 4 he died. At necropsy a carcinoma was found in the left lower lobe bronchus with extensive secondaries in the bones, suprarenals, peritoneum, and kidneys. The stomach showed two small chronic lesser-curve gastric ulcers and a small polypoid mass on the greater curvature, "which appeared histologically to be a secondary from an oat-celled carcinoma of the bronchus."

Apart from the greater risk of dying from carcinoma of the stomach following a perforated gastric ulcer, there was little difference between the two groups in the course of the disease during the follow-up period. The outstanding fact was the generally poor prognosis. Of 138 patients followed up, 29 died, including 7—that is, 5% of all the patients—who died of their ulcers. The proportion dying from peptic ulcer is far higher than would be expected to occur in a normal population, and an additional 5% mortality within an average of six years is an important consideration in the assessment of the effects of treatment, when the immediate mortality is as low as it now is.

Of the 109 patients known to have survived at the time of follow-up, 36 (33%) had been subjected to a further gastric operation. In Table X the patients have been sub-

TABLE X.—*Late Prognosis among Survivors from Perforated Peptic Ulcers, Subdivided by Sex and Age of Patient, Length of History, and Previous Diagnosis of an Ulcer*

Characteristic of Patient	Further Gastric Operation During Follow-up Period		Test of Significance of Difference
	Yes	No	
Sex:			
Males	27 (30%)	64 (70%)	$\chi^2 = 2{\cdot}808$
Females	9 (50%)	9 (50%)	$n = 1$
			$0{\cdot}05 < P < 0{\cdot}10$
Age:			
Under 45	17 (33%)	34 (67%)	$\chi^2 = 0{\cdot}0040$
45 and over	19 (33%)	39 (67%)	$n = 1$
			$0{\cdot}90 < P < 0{\cdot}95$
Length of history:			
1 year or less	7 (18%)	31 (82%)	$\chi^2 = 5{\cdot}627$
More than 1 year	29 (41%)	42 (59%)	$n = 1$
			$0{\cdot}01 < P < 0{\cdot}02$
Previous diagnosis of an ulcer:			
Yes	21 (50%)	21 (50%)	$\chi^2 = 8{\cdot}899$
No	15 (22%)	52 (78%)	$n = 1$
			$P < 0{\cdot}01$

divided in a number of ways to see whether it is possible to define simply the class of patient likely to require further operation.

Length of history and diagnosis of the presence of an ulcer before the perforation occurred seem to be the two most useful criteria. Forty-one per cent. (29/71) of the patients who survived and who gave a history of dyspepsia of more than one year and 50% (21/42) of the patients in whom the presence of an ulcer had been proved before the perforation occurred were operated on again during the follow-up period. On the other hand, only 18% (7/38) of the patients who gave a history of dyspepsia of one year or less and 22% (15/67) of those in whom the presence of an ulcer had not been proved before the perforation were re-operated on. The sex and age of the patient did not

give much indication of the subsequent course of the disease, but the number of cases in women was small, and it is possible that a sex difference would be revealed by larger numbers. Looked at from the point of view of freedom from symptoms, similar results are obtained. The sex and age of the patient seem to be unimportant, but 32% (12/38) of the patients with histories of one year or less remained symptom-free against 20% (14/71) of those with longer histories, and 30% (20/67) of those who had not had an ulcer diagnosed previously remained symptom-free, against 14% (6/42) of those who had. It can be concluded that symptoms which had lasted for more than a year or which had been severe enough to result in an ulcer having been already diagnosed before the perforation occurred are indications that the course of the ulcer disease will be unsatisfactory if the perforation is treated by simple closure.

Discussion

In recent years immediately good results have been reported with each of the three main methods of treatment; examples are shown in Table XI. The two series

TABLE XI.—*Immediate Results of Different Methods of Treatment: Recent Series*

Authors	Period of Admission	No. of Cases	No. of Cases Treated by:			General Fatality Rate
			Gastric Aspiration	Surgical Closure	Immediate Partial Gastrectomy	
Taylor (1951) ..	1946–50	73	72	1	0	9·6%
Heslop, Bullough, and Brun (1952)	1947–51	110	104	6		8·2%
" "	1946–50	124	20	104	0	9·7%*
Present authors ..	1947–51	340	20	301	19	7·9%
Nuboer (1951) ..	1947–50	65	3	0	62	6·2%
Lowdon (1952) ..	1951	65	1	13	51	6·2%

* Including one death from haematemesis a few days after suture of the perforation, excluded from the fatality rate reported by the authors.

reported by Heslop, Bullough, and Brun are of particular interest for comparative purposes, as the patients were treated in neighbouring hospitals. The authors commented that "the two surgical departments of the hospitals concerned are both engaged in general surgery, are roughly the same size, they receive their patients from the same general practitioners of the area, and one of us is the connecting link between the two hospitals in that he is on the staff of both." The separate fatality rates for the groups of patients selected for the different forms of treatment differ greatly—for example, only one death occurred among the 132 patients treated by immediate partial gastrectomy—but the immediate overall fatality rates are strikingly similar.

In these circumstances conclusive evidence of the superiority of one or other method is likely to be obtained only by means of a controlled trial which, because of the low fatality rate now associated with all forms of treatment, would need to be very extensive. In the published reports the low fatality with immediate partial gastrectomy must be partly due to the selection of good-risk cases for operation, just as the high fatality with medically treated cases is often due to the limitation of the method of treatment to patients who are already moribund. We believe, however, that it may be wrong to consider the three possible methods of treatment as rivals; if the maximum immediate and late benefit to the patients is to be achieved, all three may well have a proper place in every series. In our opinion, tentative conclusions about the indications for each method of treatment are justifiable on the basis of the existing evidence. We assess them as follows.

Medical treatment has not been reported to provide a notably better immediate prognosis than the standard surgical treatment; it does not permit patients to be selected for immediate partial gastrectomy after inspection of the ulcer, and there is no reason to suppose that the late prognosis is any better than that achieved by simple surgical closure. The method is contraindicated in the presence of bleeding or of pyloric stenosis, for a perforation after heavy eating or drinking, and in air-swallowers. Tanner (1951) sums up as follows: "The non-operative treatment demands frequently repeated expert clinical and radiological assessment, and any error in gastric aspiration, any momentary neglect, any lack of skilful observation, may be followed by disaster for the patient. . . . It is only safe in the hands of the enthusiast with ample medical and nursing assistance and is not suitable for routine usage." The method has been shown to be practicable, and is preferable when: (*a*) efficient surgery is not readily available; (*b*) other associated diseases —for example, recent coronary thrombosis—greatly increase the risk of surgery; and (*c*) perforation has occurred at gastroscopy, when the stomach is empty; for experience has shown that the perforation in this last group is often no longer detectable by the time laparotomy is performed.

Immediate partial gastrectomy has been shown to be a practicable method of treatment, compatible with an excellent immediate prognosis. As most ulcers which perforate acutely are on the anterior wall of the duodenum, the operation is technically easier to perform as an emergency for perforation than for bleeding, when the ulcers are often posterior and penetrating. It is the method of choice *for a surgeon experienced in the technique* when: (*a*) the perforation is gastric, and, although the ulcer may appear simple, there is in fact a considerable risk that it may hide an unrecognized carcinoma; (*b*) the patient gives a history of more than one year's dyspepsia and an ulcer has been diagnosed previously (because a high proportion of such patients will require a further operation if treatment is limited to simple closure); or (*c*) perforation and haemorrhage from an ulcer occur concomitantly.

We do not think it likely that immediate partial gastrectomy will be shown to be the method of choice for all perforations. It is possible that the immediate prognosis may be even better than that with simple closure of the perforations, by eliminating the deaths due to further complications arising from the persistence of the ulcer; but we have little firm knowledge of the ultimate results, and several reports have suggested that it may predispose to pulmonary tuberculosis (Pulvertaft, 1952). We do not, therefore, think that the operation can be justified as a routine procedure in duodenal ulcer patients in whom the ulcer has never previously been diagnosed and in whom the late prognosis with simple closure is reasonably satisfactory. Particularly is this so when the patients have no memory of prolonged discomfort from their ulcers to set against the symptoms of the dumping syndrome (should they arise).

Surgical closure of the perforation is now a highly satisfactory method of treatment, so far as the immediate prognosis is concerned. It is reasonable to continue to use it in the absence of positive indications for either of the other methods.

Summary

A series of 715 patients with perforated peptic ulcers, admitted during the period 1938–51, is reported.

Since 1947 there does not seem to have been any appreciable change in the fatality rate; in 340 cases, including those undiagnosed till after death, it has been 7.9%. Twenty patients were not operated on, mostly because the condition was not diagnosed or the patient was too ill; 17 died. In 301 patients simple surgical closure was carried out; 10 died, giving a fatality rate of 3.3%. Nineteen patients were treated by immediate partial gastrectomy without a death; in the first six months of 1952 the number so treated has been increased to 30. The concurrent association of haemorrhage and perforation was successfully treated by both simple closure and by immediate partial gastrectomy.

Seventy-four patients treated by simple closure for perforated gastric ulcers and an equal number of com-

parable patients with perforated duodenal ulcers were followed up after two to twelve years. Ten patients could not be traced. Eight (11%) of the "gastric" patients, but none of the "duodenal" patients, are known to have died of carcinoma of the stomach. Seven (5%) of all the patients died of peptic ulcer.

The late prognosis among the known survivors was unaffected by the sex or age of the patients or the site of the ulcer. It was affected by the length of history prior to the perforation and by whether or not the ulcer had been previously diagnosed; in the latter group 50% suffered a further gastric operation.

The advantages and disadvantages of the three current methods of treatment are discussed, and it is concluded that no one method should be the method of choice in all cases. In any one series all three methods have their proper place. Tentative conclusions about the indications for choice of method in individual cases are suggested.

We are most grateful to our colleagues at the Central Middlesex Hospital for permission to refer to cases treated under their care, and to Mr. J. D. Fergusson, Mr. F. A. Henley, and Mr. T. G. I. James for their advice in the preparation of this paper.

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GRANULOMA OF THE NOSE AND PERIARTERITIS NODOSA

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[WITH SPECIAL PLATE]

From case reports published during the past twenty-one years there gradually emerges the picture of a peculiar syndrome consisting of a chronic ulcerating granulomatous inflammation of the nose, nasal sinuses, and often pharynx, larynx, and trachea, which is followed after a time by generalized periarteritis nodosa, and which leads almost invariably to a fatal issue.

The dominant lesion at the outset of the disease causes a purulent discharge from the nose, which is usually also obstructed. The nasal mucosa presents a characteristic picture of ulcers with yellow crusts which bleed on removal, and necrosis of the bone may appear later. These symptoms are usually accompanied by low-grade fever, and within a few weeks the patient is obviously becoming seriously ill, with albuminuria, signs of renal and cardiac failure, and a rising blood urea. The terminal illness is usually short, death occurring about six months after the onset of the nasal lesions. Necropsy shows characteristic lesions of periarteritis nodosa in many organs.

This syndrome was first described in 1931 by Klinger (1 case), and since then by Wegener (1939), 3 cases; Lindsay, Aggeler, and Lucia (1944), 1 case; Weinberg (1946), 1 case; and Howells and Friedmann (1950), 1 case. Four of these patients were males and three females; their ages ranged from 23 to 70, and the total duration of illness from six to thirteen months. In all of them the post-mortem findings confirmed the diagnosis.

We record here two cases of this syndrome seen recently. In both of these a diagnosis was made comparatively early in the course of the disease—in the first case on the microscopical appearance of the nasal granuloma, and in the second on account of the striking similarity of the nasal lesions to those seen in the first case.

Case 1

A bus inspector aged 49 was admitted to St. Nicholas Hospital, Plumstead, under the care of Mr. L. E. Gardiner, on June 18, 1951, for investigation of bilateral nasal obstruction, nasal discharge, and an aching pain over the nose of three weeks' duration. There was nothing relevant in his past history, and he had not been given sulphonamides.

Examination showed slight generalized swelling of the nose externally and a thick, blood-stained discharge; the nasal mucosa was widely ulcerated, and had a raw granular surface, covered in parts with a yellow crust. It bled easily when touched; there was no fetor. The patient's general condition was good apart from a slight pyrexia and some malaise. An *x*-ray film of his nasal sinuses was clear. A course of penicillin injections, 300,000 units daily for 12 days, cleared up the discharge, but did not heal the mucosal ulceration.

A biopsy of the nasal mucosa on June 25 showed appearances interpreted as possibly tuberculous, and an *x*-ray film of his chest on July 6 revealed tuberculous apical lesions of doubtful activity on the right side. He was given a course of streptomycin, 0.5 g. twice daily, for five weeks, with P.A.S.

Persistent failure to find the tubercle bacillus in the sputum led to revision of the diagnosis, and a further nasal biopsy (Special Plate, Fig. 1) on July 16 was sent to one of us (M. O. S.) and reported on as follows: "The material consists of fragments of granulation tissue containing a fair number of eosinophils, and a small number of multinucleated giant cells of foreign-body type and of Langhans's type. There are no areas of caseation, and no tubercle bacilli have been demonstrated; one cannot at this stage entirely exclude tuberculosis, but the condition this resembles most is not tubercle but the so-called 'giant-cell granuloma of nasal sinuses.' This condition has been reported as a presenting lesion in patients who have subsequently developed periarteritis nodosa."

At the beginning of August the patient developed slight left exophthalmos, and another *x*-ray film of his sinuses showed left antral infection. Mucopus containing *Staph. pyogenes* and pneumococci was washed out at puncture. Subsequently a muscle biopsy from the thigh showed a small acutely inflamed artery, confirming the diagnosis of periarteritis nodosa (Fig. 2). By the second half of August he had developed gross oedema of the limbs and a peripheral neuritis of the mononeuritis multiplex type. He became severely breathless with left ventricular failure, and a chest *x*-ray film showed "bat's wing" changes in the mid-zones. Throughout this illness the nasal picture was unchanged.

He was transferred to Lewisham Hospital on August 28 for A.C.T.H. treatment; three intravenous infusions, two of 30 mg. and one of 50 mg., were given without apparent benefit. He died on September 1.

Investigations.—July 19: E.S.R., 52 mm. in first hour (Wintrobe 100-mm. tube). August 5: haemoglobin, 8.89 g.%; red cells, 2,800,000 per c.mm.; white cells, 8,000 per c.mm. (polymorphs 72%, lymphocytes 26%); M.C.H., 31 γγ; M.C.D., 7.2 μ; E.S.R., 61 mm. in one hour. August 14: urine contained 40 mg. of protein per 100 ml. and a few red and white cells. August 27: haemoglobin, 7.96 g.%. August 29: blood urea, 84 mg. per 100 ml. Blood-pressure readings: July 18, 160/80; August 17, 180/120; August 28, 155/90.

Necropsy Findings.—Externally, oedema of legs. The heart showed hypertrophy of the left ventricle; all main arteries were healthy. Nasal, laryngeal, and tracheal mucosae were hyperaemic, and one minute granulomatous nodule was present in the tracheal wall. The lungs were airless, oedematous, and congested; there were a few thrombi in the terminal branches of the left pulmonary artery and a small caseous tuberculous focus at the left apex. Pus was present in the antra and ethmoid sinuses. The left kidney had a small infarct; many other organs showed effects of heart failure but were otherwise normal.

Histology.—Kidney: many glomerular tufts contained small fibrin thrombi and showed minute foci of fibrinoid necrosis of the capillary loops, with rupture and small haemorrhages into Bowman's capsule. In some places there were adhesions between the tufts and the capsule, and early crescent formation was present. A small recent infarct was present in the left kidney. No acute arteriolitis was seen, but an acute necrotizing arteritis was occasionally present. Other acute arteritic lesions, typical of periarteritis, were seen in the capsule of the adrenals, the lungs, a small branch of the left coronary artery, and one of the vasa nervorum of the left anterior tibial nerve. The mucosae of the maxillary antra showed inflammatory reaction, with only one giant cell.

Case 2

A maintenance worker aged 51 was first seen on August 13, 1951, with a three-months history of nasal catarrh and obstruction, mild earache and deafness, a husky voice, and some loss of weight. There was no record of his having had sulphonamides before coming to hospital. His general condition was good. The nasal mucosa was congested without ulceration or crusting, there was mucopus in his nasopharynx, and he had chronic laryngitis. An *x*-ray film showed infection of the left maxillary antrum, which was punctured on three occasions, some smelly pus being washed out each time.

Not much improvement resulted from these measures, and on September 21 a raw granular area, without crusting, was seen on the mucosa of the left side of the septum. A biopsy of this showed thickened transitional epithelium and underlying connective tissue with slight chronic inflammatory reaction. At about this time he began to feel ill, with night sweats, cough, and occasional rigors. Except that he looked ill and thin, a general examination on September 29 did not show any abnormal physical signs, apart from his E.N.T. condition.

He was admitted to St. Nicholas Hospital on October 4, as he had by then developed pains and weakness in his limbs. His septal mucosa was extensively ulcerated, and was covered with dirty yellow crusts which caused bleeding on removal. His tongue was red, smooth, and dry, and his pharynx injected and covered with sticky mucus. The appearance of the nose was so like that in Case 1 that a provisional diagnosis of periarteritis nodosa was made; in keeping with this, he was found to have a widespread mononeuritis multiplex, involving all four limbs in a flaccid paralysis with equivalent sensory loss, and associated with considerable oedema. He also had a tachycardia; rales could be heard throughout both lungs; and an *x*-ray film showed "bat's wing" shadows in both mid-zones. The diagnosis was confirmed by muscle biopsy.

Later, a second biopsy of his nasal mucosa showed scanty lymphocytic infiltration but no giant cells. As a further antrum puncture still produced a little pus, a polythene tube was inserted for penicillin irrigation. On October 23 cortisone therapy was begun at Lewisham Hospital, and he was given 100 mg. by injection twice a day until he died, uraemic and in heart failure, five days later.

Investigations.—October 23: haemoglobin, 56%; red cells, 3,120,000; white cells, 28,000 (lymphocytes 20%, polymorphs 78%, monocytes 2%); blood urea, 128 mg. per 100 ml. October 27: blood urea, 270 mg. per 100 ml. Blood-pressure readings: October 13, 190/110; October 24, 175/105.

Necropsy Findings.—Externally, some oedema of ankles. The pleural cavities had some free fluid and fibrinous adhesions. The heart showed slight right and left ventricular dilatation, but was otherwise healthy. All lobes of lungs

K. R. HILL ET AL.: LEGENDS TO PLATE

FIG. 1.—Serous exudation in liver of child aged 1½ years. (H. and E. ×150.)

FIG. 2.—Serous exudation in the space of Disse. High-power of Fig. 1. Two sinusoids are shown widely separated from the columns of liver cells by serous exudation, which has markedly distended the perisinusoidal spaces. (H. and E. ×560.)

FIG. 3.—Liver of child aged 2 years showing intralobular fibrillary collagen from previous attack and a serous exudate from current attack. (Picro-Mallory connective-tissue stain. ×600.)

FIG. 4.—Wax-like eosinophilic coagulum in a perisinusoidal space, from the liver of a child aged 4 years. The coagulum gives the tinctorial reactions of collagen. (H. and E. ×680.)

FIG. 5.—Serial section of same case as Fig. 4. Stained with picro-Mallory connective-tissue stain. Note the blue-staining coagulum in the perisinusoidal space: the sinusoid is clearly seen. (×630.)

FIG. 6.—Serial section of same case as Fig. 5, stained with modified Foote-Wilder reticulin stain: the reticulin fibres are swollen and stained black, but the "blobs" of coagulum are golden yellow in colour and are laminated. (×520.)

FIG. 7.—Liver of child aged 4 years. Stained with a modified Foote-Wilder reticulin stain. There is perivascular cuffing around the centrilobular veins with radiating perisinusoidal reticulinosis. (×600.)

FIG. 8.—Serous exudate distending the space of Mall of a portal triad in the liver of a child aged 2½ years. (H. and E. ×370.)

FIG. 9.—Liver of a child aged 2½ years, showing perivascular deposition of coagulum around an interlobular vessel extending between two portal triads. (Picro-Mallory stain. ×360.)

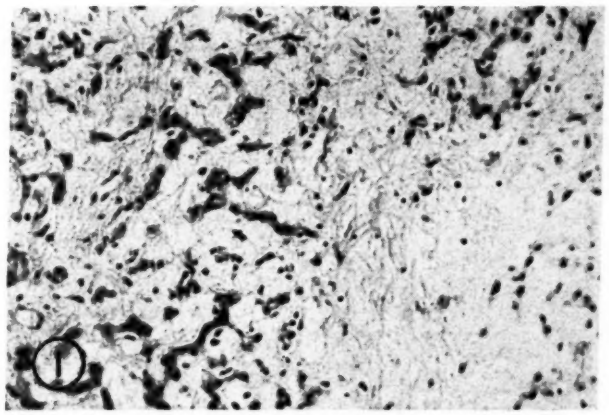
FIG. 10.—Widespread deposition of eosinophilic coagulum in the space of Disse throughout the lobule of a child aged 3 years 3 months. The coagulum has a sparse cellular infiltration indicating early fibrosis. (H. and E. ×600.)

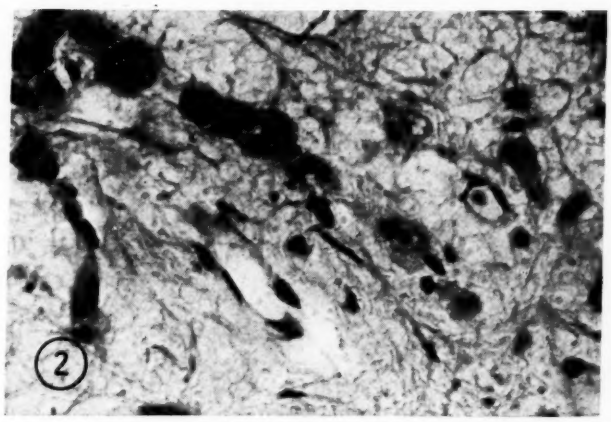
FIG. 11.—Liver from a child aged 2 years showing hepatic fibrosis; stained with a modified Foote-Wilder reticulin stain. Note the centrilobular cuffing and the perisinusoidal and perilobular reticulinosis. (×70.)

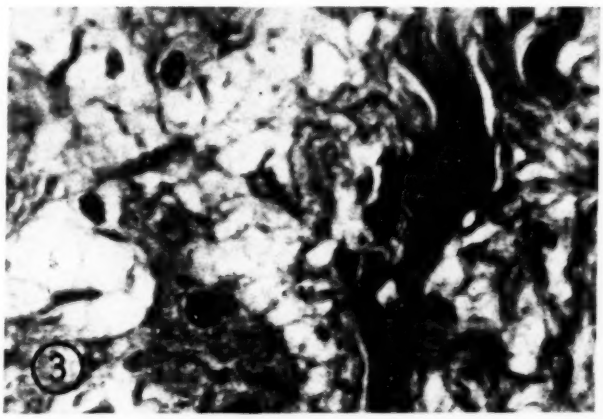
FIG. 12.—Liver from a child aged 2 years showing hepatic fibrosis. There are connecting bands between portal triads and centrilobular veins. (H. and E. ×150.)

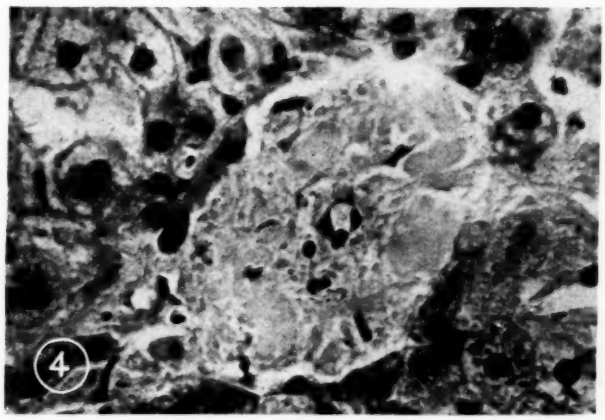
FIG. 13.—Shows marked hepatic fibrosis with lobule distortion and nodular reconstruction from liver of child aged 2 years. (Modified Foote-Wilder reticulin stain. ×140.)

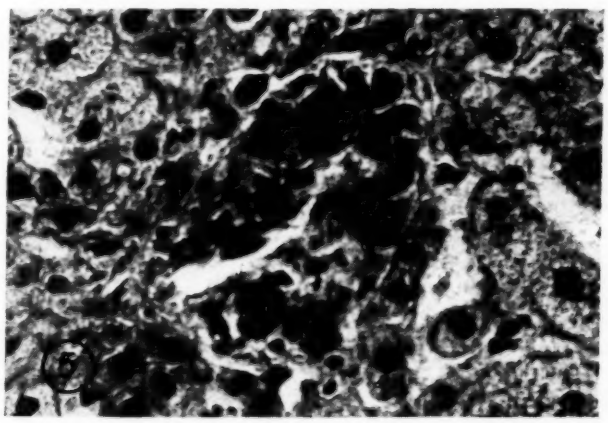
K. R. HILL, KATERINA RHODES, J. L. STAFFORD, AND R. AUB: SEROUS HEPATOSIS

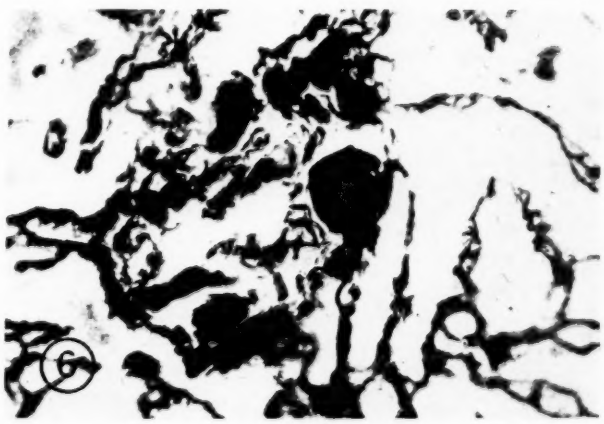


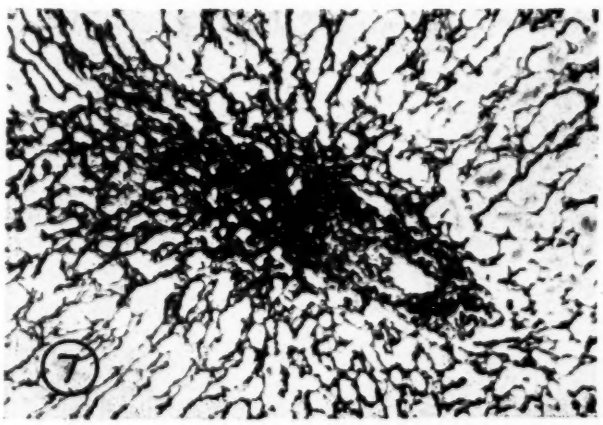


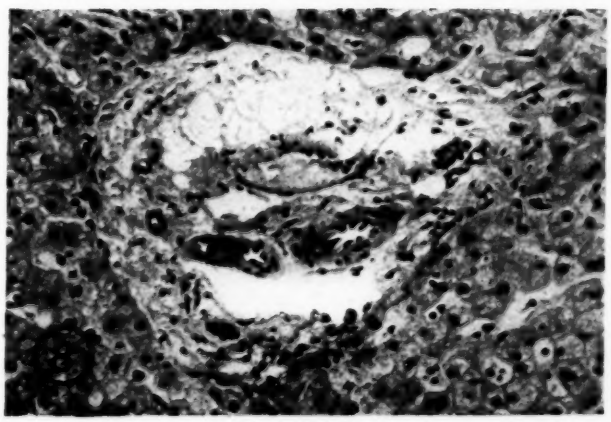




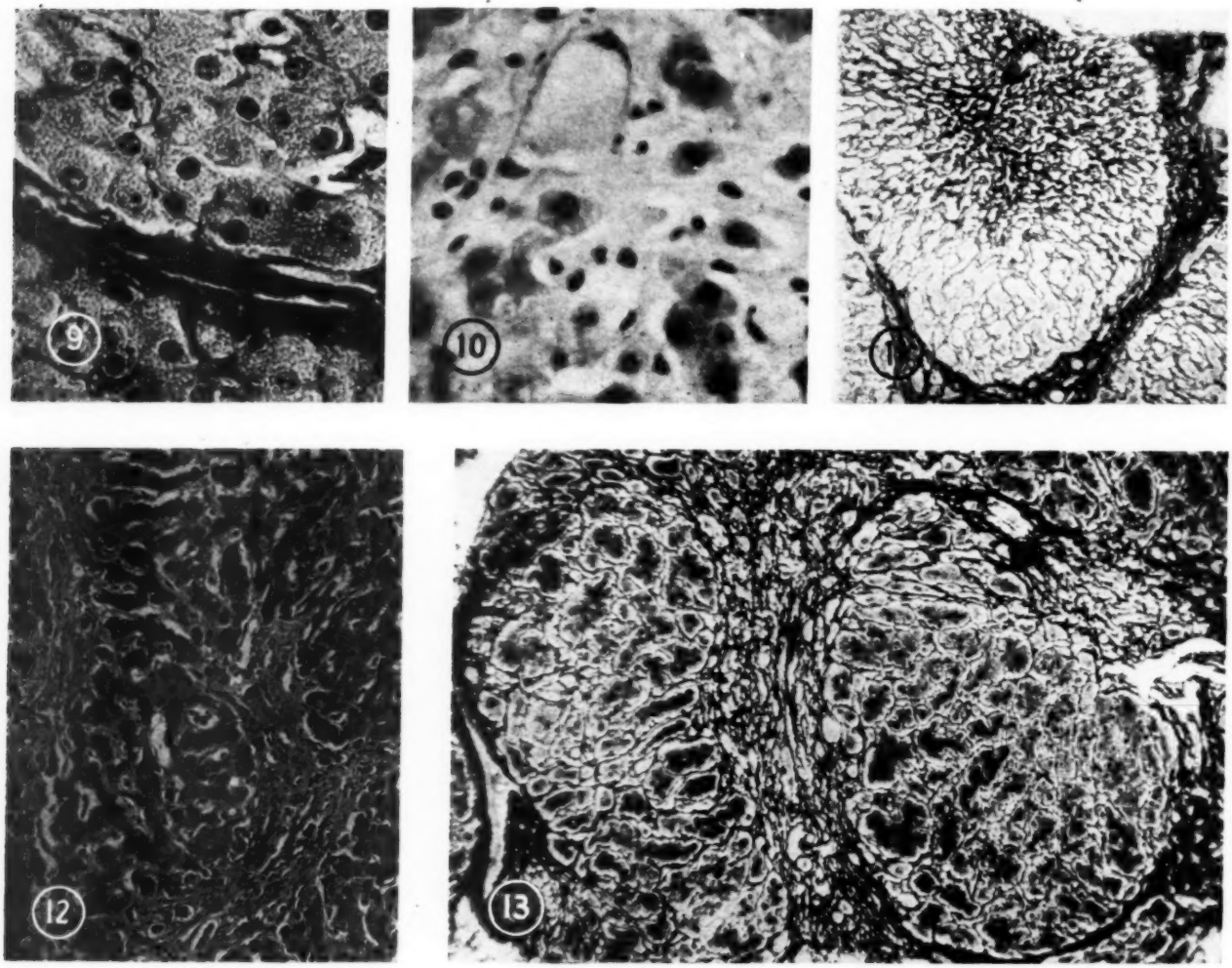








K. R. HILL, KATERINA RHODES, J. L. STAFFORD, AND R. AUB: SEROUS HEPATOSIS



H. J. M. STRATTON, T. M. L. PRICE, AND M. O. SKELTON: GRANULOMA OF NOSE AND PERIARTERITIS NODOSA

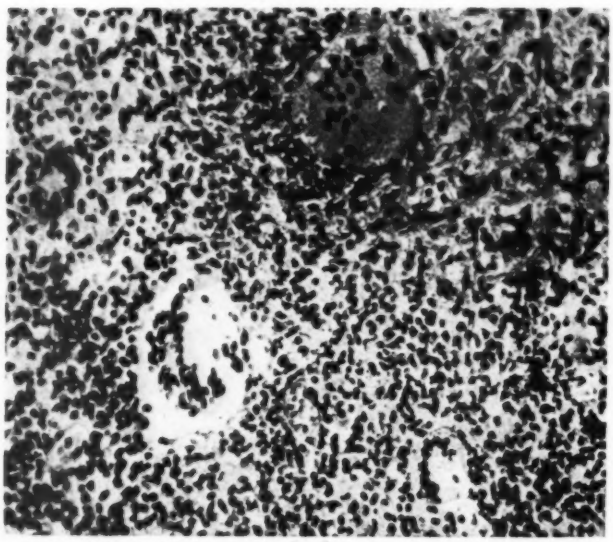


FIG. 1.—Nasal mucosa of Case 1, showing chronic inflammatory reaction and multinucleated giant cells. (H. and E. ×110.)

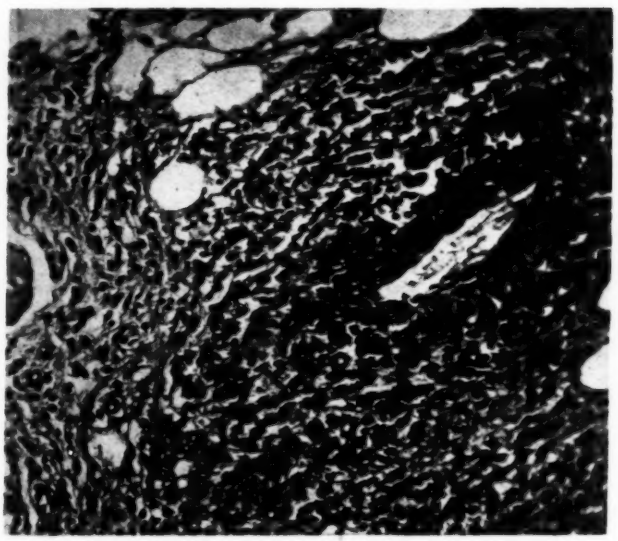


FIG. 2.—Muscle biopsy of Case 1, showing acute inflammatory reaction in wall of small artery. (H. and E. ×90.)

K. D. FORGAN MORLE AND P. W. ROBERTSON: SEGMENTAL ASPIRATION PNEUMONIA AND BRONCHIECTASIS

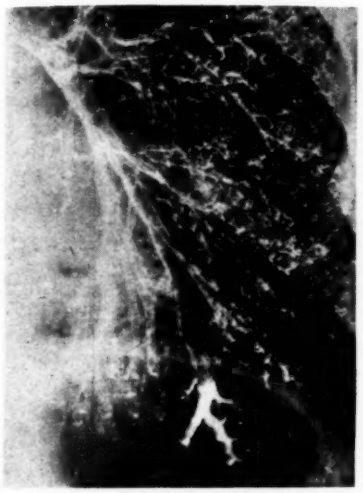


FIG. 1.—Bronchial dilatation.

FIG. 2.—Bronchial crowding.

FIG. 3.—Failure to fill bronchi in affected segment. Note heavy striate markings in unfilled region.

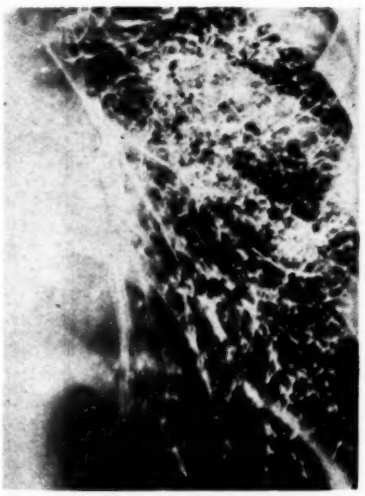


FIG. 4.—Normal bronchogram in same case as Fig. 1 after three months' physiotherapy.

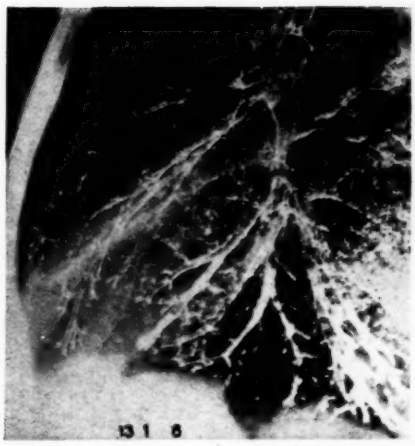


FIG. 5.—Bronchogram showing some cylindrical dilatation in all basal segments of the left lower lobe.

FIG. 6.—Bronchogram of the same patient as Fig. 5, six weeks later.

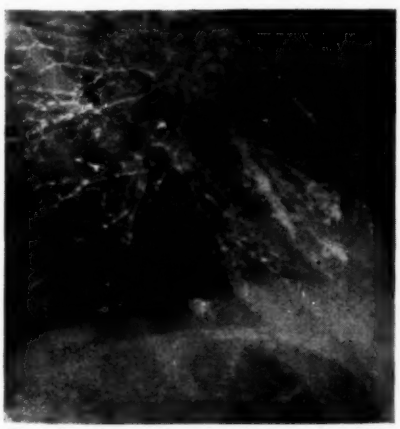


FIG. 7.—Bronchiectatic changes in right middle lobe following an acute inflammatory lesion with collapse.

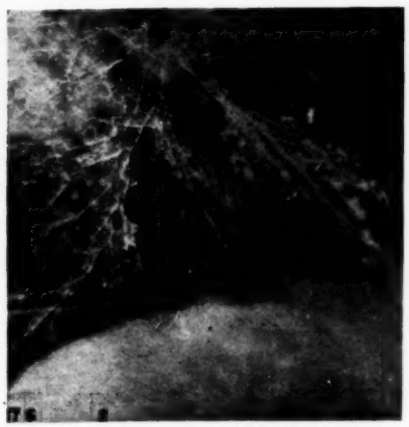


FIG. 8.—Same case as Fig. 7 one year later, showing some re-expansion of right middle lobe but persistent bronchiectasis.

FIG. 9.—Widespread bronchiectasis in right lower lobe. This patient originally developed segmental pneumonia five years previously.

T. NICOL AND A. ABOU-ZIKRY: INFLUENCE OF OESTRADIOL BENZOATE AND ORCHIDECTOMY ON THE RETICULO-ENDOTHELIAL SYSTEM

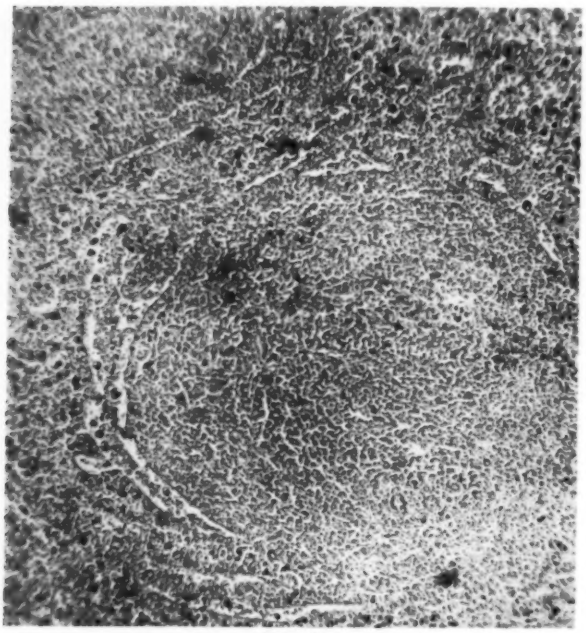


FIG. 1

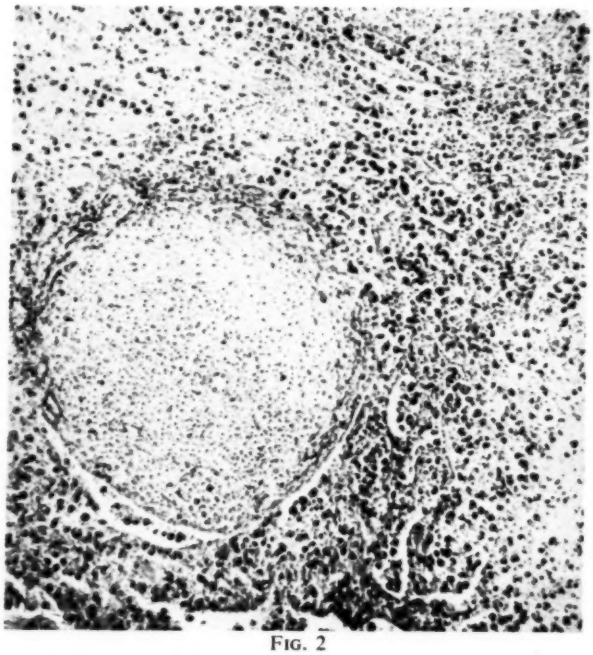


FIG. 2

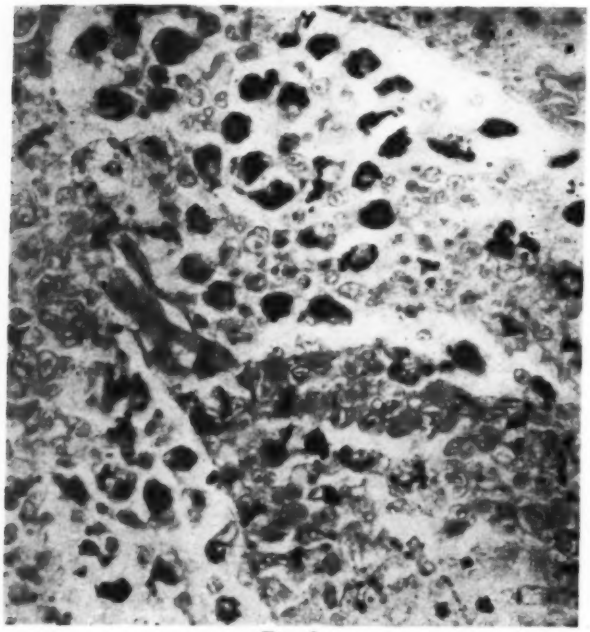


FIG. 3

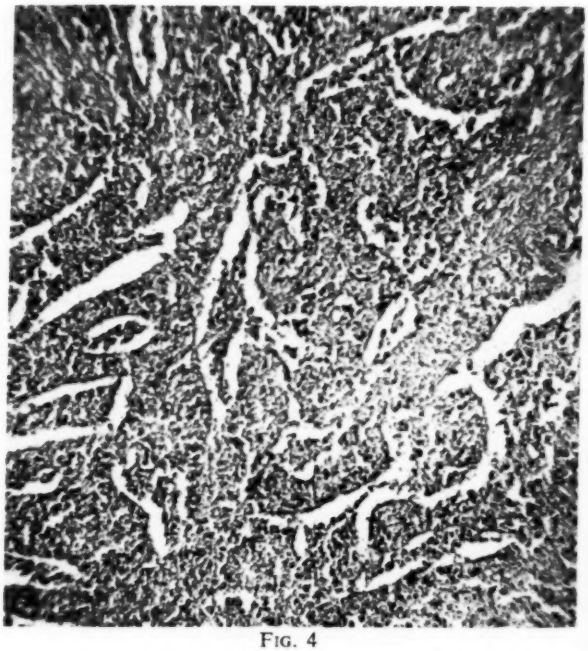


FIG. 4

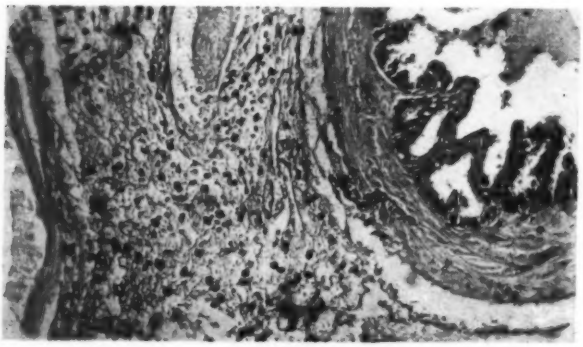


FIG. 5

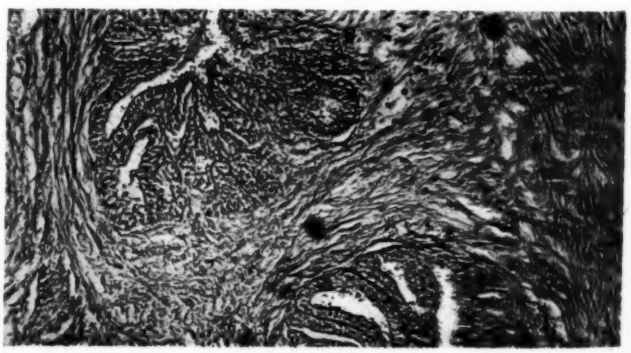


FIG. 6

showed red areas of infarction. The pancreas had two small infarcts in its tail; and the spleen showed irregular pale-pink areas throughout the pulp due to necrosis in areas of infarction. The kidneys had no macroscopic vascular nodules; there was one infarct. Periarteritic nodules were seen along small branches of the superior mesenteric and left gastric arteries. There was flat ulceration in nasal cavities—none anywhere else in respiratory tract. Microscopically the kidneys were similar to those of Case 1. Periarteritis was seen in small arteries of the kidneys, liver, lungs, mesentery, ileum, sciatic nerve, soleus muscle, and in arterioles at centres of malpighian bodies of spleen. Right antral mucosa was normal; left antrum and nasal cavities showed chronic non-specific inflammatory changes. Other body organs were essentially normal.

Discussion

As Howells and Friedmann (1950) point out, there are in the literature several cases of periarteritis nodosa in which chronic sinus infection was noted in the previous clinical history without its significance being emphasized. Upper-respiratory-tract infection probably plays a more significant part in periarteritis nodosa than is generally recognized, and the important feature of the particular syndrome here described is that it is sufficiently clear-cut to enable a diagnosis to be made early. In both our cases the subsequent development of periarteritis nodosa was predicted on the appearances of the nasal mucosa. The microscopical appearances of the fully developed granuloma with its large multinucleated giant cells (Special Plate, Fig. 1) are very striking. Giant cells, however, were not seen in the mucosa in Case 2, either in the biopsy specimen or in the fragments of nasal and sinus mucosa procured at necropsy.

The essence of this syndrome is that the upper-respiratory-tract lesions are the first, and at the outset the dominating, feature of the condition. The periarteritis nodosa picture develops subsequently. This course of events is shown in our two cases. Several cases have been quoted in the literature as examples of this syndrome which do not fulfil these criteria—for instance, the case described by Rössle (1936–7) in which the nasal lesions were incidental in the disease process and were not the initial changes; and the case of Banowitch, Polayes, and Charet (1942) in which a mediastinal mass of giant cell granuloma affected the lung and was associated with periarteritis nodosa. There were no nasal lesions in this case.

Limiting the discussion of the syndrome to those cases exhibiting upper-respiratory-tract ulceration with the subsequent development of periarteritis nodosa, one may speculate on the possible significance of this pattern of the disease process. It is a well-known theory that periarteritis nodosa results from a hyperergic antigen–antibody reaction in the tissues, particularly affecting the vessels but also leading to the development of the granulomatous lesions in the extravascular connective tissue, which sometimes show giant cells of foreign-body type. Such granulomatous lesions have been produced experimentally by Goddard (1947), in his researches on the Arthus phenomenon, by injecting egg albumen into the skin of guinea-pigs; and numerous others—for example, Klinge (1933), Bergstrand (1946), and Pagel (1951)—have described the occurrence of granulomata in the connective tissue in periarteritis nodosa and in acute rheumatism and many others of the so-called "collagen diseases"; thus the nasal lesions in this syndrome may be regarded as special types of paravascular granulomata in the sense of the term used by Pagel, and are in accord with the theory that the disease is a manifestation of hypersensitivity.

There seem to be two possible explanations of the pattern of development of this syndrome. It may be that the patients have already developed generalized periarteritis and that the nasal lesions are merely the first to become apparent. There is no evidence to show whether or not generalized periarteritis nodosa was present at the time these patients first complained of nasal symptoms, and the clinical history at least suggests that the generalized disease followed later; but the patients were not submitted to a general investigation on their first attendance at the E.N.T. department with nasal lesions, and there are no data on this point.

A second possibility is that the upper-respiratory-tract lesions represent the relatively localized site of an attack on the body defences by some injurious agent of bacterial or chemical origin, and that widespread arterial lesions develop subsequently in a body now sensitized. This view is favoured by Wegener (1939) in his survey of the condition.

Another problem concerns the possible relationship between this disease and the condition known variously as "malignant granuloma of the nose" (Woods, 1921) or "progressive lethal granulomatous ulceration of the nose" (Stewart, 1933). The majority of the cases of this disease, which is almost invariably fatal, have not been examined after death, and still fewer have been examined histologically. However, Case 1 of the six cases described by Woodburn and Harris (1951) as examples of this disease and the third of Williams's (1949) three cases showed periarteritis nodosa at necropsy. Woodburn and Harris's Case 1 had

T. NICOL AND A. ABOU-ZIKRY: LEGENDS TO PLATE

FIG. 1.—Photomicrograph of section of spleen of intact male control guinea-pig which received one subcutaneous injection of trypan blue daily at 4 p.m. for six days and was killed the following day. Shows a moderate number of dye-bearing cells in the sinuses of the red pulp. The dye-bearing cells appear black in the photomicrograph. (Weak eosin. ×200.)

FIG. 2.—Photomicrograph of section of spleen of intact male guinea-pig which received 0.5 mg. oestradiol benzoate intramuscularly daily at 10 a.m. for four weeks plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. Shows numerous dye-bearing cells in the reticulum and in the dilated sinuses of the red pulp. The dye-bearing cells appear black in the photomicrograph. (Weak eosin. ×200.)

FIG. 3.—Photomicrograph of section of spleen of intact male guinea-pig which received 0.5 mg. oestradiol benzoate intramuscularly daily at 10 a.m. for three weeks plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. Shows a large number of dye-bearing cells in a dilated sinus of the red pulp. The dye granules, which appear black in the photomicrograph, sometimes mask the nucleus of the cell. (Weak eosin. ×650.)

FIG. 4.—Photomicrograph of section of spleen of orchidectomized guinea-pig which received 0.5 mg. oestradiol benzoate intramuscularly daily at 10 a.m. for four weeks, plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. Shows sinuses of red pulp dilated and empty of cells. Only a few dye-bearing cells can be seen in the reticulum. The dye-bearing cells appear black in the photomicrograph. The splenic vein in this animal contained many dye-bearing cells. (Weak eosin. ×200.)

FIG. 5.—Photomicrograph of section of prostate of intact male guinea-pig which received 0.5 mg. oestradiol benzoate intramuscularly daily at 10 a.m. for four weeks, plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. Shows dye-bearing cells in the areolar tissue between the acini. The acini are surrounded by a thickened layer of fibrous tissue. The dye-bearing cells appear black in the photomicrograph. (Carbolfuchsin. ×200.)

FIG. 6.—Photomicrograph of section of prostate of orchidectomized guinea-pig which received 0.5 mg. oestradiol benzoate intramuscularly at 10 a.m. for four weeks, plus one subcutaneous injection of trypan blue daily at 4 p.m. during the last six days before being killed. Shows a densely fibrous prostate. The acini are collapsed and the lining epithelium is thrown into folds. (Weak eosin. ×200.)

two years' history of nasal obstruction, ultimately developing ulcerating lesions of the nose and trachea, and died after one year's illness; at necropsy an acute necrotizing arteritis was found in many organs. We feel that these two cases are perhaps examples of nasal granuloma with periarteritis, as described here.

We have been able to examine slides of nasal lesions and post-mortem specimens of four cases of classical malignant granuloma of the nose. No evidence of periarteritis nodosa was seen, and the local lesion was a chronic non-specific inflammation. Therefore we have no evidence to enable us to decide whether the classical destructive "malignant granuloma of the nose" is another manifestation of the condition previously discussed or something entirely different.

Summary

Two cases are described in which periarteritis nodosa was preceded by an ulcerating granuloma of the nasal mucosa. Seven similar cases, and possibly two others, have been collected from the literature.

The significance of the nasal lesions is discussed and the possible connexion pointed out between this condition and the so-called "malignant granuloma of the nose."

We wish to thank Mr. L. E. Gardiner for permission to publish Case 1; Dr. I. Friedmann, Dr. A. G. Stansfield, Mr. N. R. Jory, and Dr. R. H. D. Short for allowing us to see tissues from cases of "malignant granuloma" of the nose; Mr. S. E. Andrews for the photographs; and Mr. H. Eastwood and Miss K. M. Vale for technical assistance.

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The Lebanon Hospital for Mental and Nervous Disorders at Asfuriyeh, near Beirut, was opened in 1900, and since then has passed through many excitements and upheavals, but the work has gone on unbroken. Apart from a financial crisis during 1946–7, the hospital has grown steadily, the peak number of in-patients being 501 during the summer of 1938. There are now some 23 buildings (contributed by four countries) on an estate of 38 acres beautifully situated on the foothills of Mt. Lebanon, about five miles from Beirut. The present number of beds is 450, but, with the opening this year of a large new building, there will again be room for 500 patients. The latter come from 14 or 15 countries and are of a dozen different religions. They are of all types and classes, from the rich to the destitute. The hospital also runs a neuropsychiatric clinic in Beirut, which is doing important work for early cases. Developments since 1948 include a training school for Lebanese and Near Eastern student nurses, with an Asfuriyeh certificate in psychiatric nursing. Psychiatric instruction to doctors is of longer standing, and the present medical director, Dr. W. M. Ford Robertson, is clinical professor of psychiatry at the American University of Beirut, and two senior psychiatrists also share in the work of teaching. There are also special courses at the hospital for graduate doctors and nurses of various nationalities. A copy of the annual report of the hospital can be obtained on application to the Lebanon Hospital office, Drayton House, Gordon Street, London, W.C.1.

SEGMENTAL ASPIRATION PNEUMONIA AND BRONCHIECTASIS*

BY

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AND

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[WITH SPECIAL PLATE]

In a previous publication we described the clinical features of a large series of cases of segmental aspiration pneumonia (Robertson and Morle, 1951) and suggested that the syndrome of primary atypical pneumonia could be largely explained on an aspiration basis. Reference was then made to bronchographic studies undertaken in these cases of segmental pneumonia. It was stated that a wide range of bronchial abnormality might occur within such lesions and that these changes might be serious and sometimes irreversible.

These changes are now described and their significance is discussed in relation to the natural history of bronchiectasis.

So far we have carried out bronchography about 600 times on over 300 cases of segmental pneumonia. From so large a series we feel that enough evidence is forthcoming to substantiate our view that many, if not most, of the cases of bronchiectasis originate from these segmental pneumonias occurring in association with upper respiratory infections.

Bronchograms

There are many degrees of deviation from the normal, and in a few borderline cases it has been found difficult to decide whether a bronchogram was abnormal or not. This difficulty, which appears to have worried other authors (Evans and Galinsky, 1944), is a matter of some importance, as changes of such minimal nature may represent the initial stages of disease, which may later become fully established.

We classified a bronchogram as abnormal if one or more of the following features were present. (*a*) Dilatation: this varied in degree from minimal changes in calibre to gross and obvious dilatation. (*b*) Crowding: approximation and crowding together of the bronchial shadows. (*c*) Failure to Fill: failure to obtain satisfactory filling of the peripheral bronchi of the region studied.

Further features noted in those bronchograms classified as abnormal on the basis of the above three criteria included distortion and angulation of the peripheral bronchi and apparent irregularity of the bronchial walls. Some elucidation of the three main abnormal features is perhaps necessary.

Calibre changes vary from loss of the normal degree of taper of the bronchus as the periphery is reached to severe and obvious dilatation. In an estimation of the significance of an apparently dilated bronchus there are several features to be taken into consideration. An illusion of dilatation may be caused by solid filling of a group of bronchi. Allowance must be made for the magnification of the

*The substance of this work formed a paper given at a meeting of the Thoracic Society in July, 1951.

image of the bronchus due to the distance of the latter from the film. In serial films care must be taken to allow for physiological change in calibre occurring at different phases of respiration.

Bronchial crowding is easily recognized, and is of course due to some degree of collapse. The coexistence of bronchial dilatation with bronchial crowding is well known and extremely common (Lander, 1946).

It is characteristic of bronchography that the appearances produced are transitory and that different stages of filling are recorded on serial films (Di Reinzo, 1949). For this reason it is unwise to be content with single films, and where necessary these should be followed by additional films after further posturing.

In general, a normal bronchial tree can be completely outlined without difficulty, and persistent failure to fill suggests bronchial abnormality. For this reason it is not possible to interpret bronchograms showing incomplete filling due to inadequate technique.

Bronchography performed in the presence of a resolving segmental aspiration pneumonia will usually show failure of filling of the peripheral bronchi within the affected segment. Further, there may be damming up of the lipiodol in the more proximal portion, indicating blockage of the peripheral bronchi by exudate. Persistent attempts to fill such a segment may lead to well-marked normal alveolar filling in surrounding normal regions—the affected region, in which neither the bronchioles nor the alveoli are filled, then being clearly demarcated. The inconstant changes referred to as rippling or beading of the outline of the bronchial wall could not be relied upon as an indication of abnormality.

The frequency with which the various bronchographic abnormalities are demonstrated in segmental aspiration pneumonia is closely related to the stage in the illness at which the bronchogram is done. Thus the incidence of abnormality is greater in the earlier stages of the illness; reversion of the bronchographic change tends to occur as resolution and re-expansion take place. The three main types of bronchographic abnormality mentioned above usually coexist, though any one may predominate over the others at different stages of the illness.

It is therefore of little value to express statistically the percentage of cases showing bronchographic abnormality. Any such figures would be wholly inaccurate and misleading. Even the incidence of persisting bronchial change is difficult to determine, for this depends upon the length of follow-up, the efficacy of treatment, and the possibility of some pre-existing disease in the affected segments. As a general impression from the investigation of over 300 cases it is felt justifiable to give a figure of about 60–70% as the incidence of bronchial abnormality in all cases of segmental aspiration pneumonia. Possibly about 5% of such pneumonic lesions have led to established bronchial abnormality despite adequate therapy and observation over a period of 18 months to two years. It is not known what the last figure would be if the cases were untreated, but it would probably be very much higher.

Natural History of Bronchiectasis

In this particular series, dealing as it does with chest infections and various stages of bronchiectasis, a history of previous significant chest illness would normally be regarded as of great importance, but in our experience it has proved unreliable. The difficulty centres on the word "significant." There can be few members of the general population who do not admit to winter coughs and colds, but these are not regarded as significant by either patient or general practitioner. Most of the present series gave a history of no more significant previous illness than such conditions, though 15% gave a history of "pneumonia." In some instances this previous history, together with a recent illness, led to the performance of bronchography on the supposedly affected side. It is interesting to note that the percentage of abnormal bronchograms in such cases was little different from that of cases with no past history of chest disease.

One is continually faced with difficulty in interpreting the accuracy of the history: What does the patient mean by pneumonia? What does he mean by a chest cold? Doubtless in many cases either of these may have been an illness of the type described here. The patient will occasionally state that he has never had a chest illness but that he has had an illness similar to his present condition, in which there are chest pain and cough and radiological changes. There is therefore much unreliable material in the patient's history.

When one takes into account the more nebulous "chesty" colds and coughs a somewhat similar picture is evident. In approximately 13% of all cases such a history was given, and it was found that 79% of these had abnormal bronchograms. This latter group actually includes most of the more severe lesions. However, most of those with gross established and widespread bronchiectasis did not give a history which one might regard as typical of that condition and certainly no more suggestive than many who were shown to have normal bronchograms.

There are three principal points which it is wished to stress in connexion with the previous history of illness. (1) In most instances a history of a specific illness such as pneumonia is of no certain value other than indicating that there has been a chest illness. The diagnosis may well have been made on scanty evidence. The site and type of pneumonia are rarely known to the patient, and there is always the tendency for him to have received an exaggerated version of the childhood illness from his mother. (2) Although it was found that a high percentage of patients with a history of chest colds did show bronchographic evidence of disease, it must not be imagined for a moment that the history was definite enough to enable one to pick it out as "significant" as compared with the histories of a large group of general medical patients. (3) In any individual case only a survey of recent events was of help in deciding upon what investigations were necessary.

It is important to try to ascertain the age of any bronchial abnormality demonstrated in a pulmonary segment which has recently been the site of an inflammatory process. One must determine whether or not the inflammatory process was superimposed upon a pre-existing bronchial lesion. This point has been discussed from a slightly different angle by Grier (1944) and Scarlett (1946), who referred to the possibility of confusing primary atypical pneumonia with bronchiectasis which is the site of a pneumonic exacerbation; and from yet another angle by Blades and Duggan (1943), who stated that bronchograms obtained after atypical pneumonia may occasionally be misleading and give the impression that the condition was true bronchiectasis. They showed that in several instances such bronchiectases reverted to normal, and they attempted to differentiate this from true bronchiectasis on clinical criteria. They do not seem to have appreciated, as did Ogilvie (1941), that this was an early stage in the natural history of bronchiectasis.

It is our view that in most instances the bronchial condition developed during the current illness. There are several points in support of this opinion: (1) so many of the patients could give no history of chest illnesses of any kind, however trivial; (2) all cases had been passed by mass miniature radiography examination within the previous few weeks; and (3) further evidence is provided by the demonstration of reversion to normal. Failure to conform to any one of these points must cast doubt on the age of the bronchial lesion.

This statement that the bronchial condition usually developed during the current illness is of fundamental significance. It indicates that illnesses such as the so-called "primary atypical pneumonia" syndrome can give rise to serious structural abnormalities within the affected segment. The fact that such structural abnormalities are

concealed calls for great care in the handling of these cases. It provides the reason for the persistence of symptoms or signs after an apparently straightforward "virus pneumonia"; it disposes of the fallacy that such illnesses are necessarily benign; and it offers a demonstration of the actual development of bronchiectasis.

The Forerunner of Bronchiectasis

What place in the natural history of bronchiectasis does this process occupy? It is our belief that this sequence of events is the forerunner of many cases of bronchiectasis. The importance of this statement lies in the appreciation of the commonness of segmental collapse and such illnesses. It has, of course, long been recognized that there is a close relationship between bronchiectasis and such collapse (Findlay, 1935; Andrus, 1937; Lander, 1946). It has not, however, been generally recognized that such atelectatic lesions are so frequent and that most of them may arise from an aspiration mechanism, as has been suggested by us. Such aspirated material is not necessarily derived from the upper respiratory tract, for local bronchial plugging may occur from failure to clear excessive bronchial secretion, as in generalized bronchitis or in asthma. Perhaps rather too much emphasis has been placed on glandular compression, foreign bodies, carcinoma, etc., which are well known to give rise to bronchiectasis but are infinitely less common. Furthermore, we believe that this type of illness forms most of the "bronchopneumonic" illnesses of childhood, the lesions being similar to those described by Lees (1950) in association with pertussis.

In some cases we have been able to observe that where there have been recurrent inflammatory episodes increasingly severe bronchial damage follows. This is suggestive of the possible course of the development of bronchiectasis.

Where obviously established and gross bronchiectasis is found, it is sometimes possible by careful history-taking or by inspection of Service medical documents to reveal an initial illness such as we have described. This may have been four to five years previously and at that time thought to be of little significance, but recurrent chest episodes of increasing severity and frequency followed. We believe that such a history is not that of infection superimposed on previously dilated and damaged bronchi but that of the gradual development of the condition. Finally, and, we feel, most significant of all, the site incidence of segmental pneumonia is identical with that of established bronchiectasis (Robertson, 1951).

Some Problems

Many problems are raised by the detection of segmental bronchial abnormality in a healthy relatively symptomless young man. Little guidance can be obtained from the literature for the long-term management of such cases, and, so far, our own experience has been limited to a three-years study.

In the management of such cases it is often most difficult to correlate the bronchographic changes with the patient's clinical state. How is one to foretell the local anatomical prognosis? Will it remain the same, or improve, or get worse? Having attempted to answer this, one then asks how the patient will be affected clinically. It is only the experience we have gained from serial bronchography on our earlier cases which has given us guidance on the likely course of the local lesion. For example, the segmental lesion may not clear radiologically and the patient may or may not have persistent symptoms; the segment may clear radiologically but troublesome symptoms remain; then, again, there may be apparent recovery radiologically and clinically, but the whole sequence may recur.

The object in all cases in which a segmental lesion has been recently demonstrated should be to arrange for a period of at least six months' observation and treatment. Bronchography should be employed as a guide to progress. In our own work we have usually performed bronchography a second time at the end of about six to eight weeks, and, if still abnormal, again after four to six months. Most of our patients did in fact show reversion at the time of the first or second repeat bronchogram, and these have not appeared to be particularly prone to further trouble.

One of the most difficult types of case to handle is that in which bronchial damage can be persistently demonstrated but in which symptoms are so often minimal; such a condition might, under normal conditions, and remaining uninfected, be undetected for many years.

When the question of surgical treatment is raised there are again a number of points to consider. What is the risk of recurrent "pneumonia"? Is further damage likely to occur in the same or in adjacent segments? So far as the question of spread is concerned we have been able to show that further damage in the same or neighbouring segments can, and does, occur with the passage of time, although such spread may in turn be reversible if recognized.

Would it be justifiable to interfere surgically in the hope of avoiding more widespread disease with disabling symptoms in, say, 10 years, at which time conditions might be unfavourable for operation? The only patients of ours who were finally selected for local segmental resection with this in mind refused operation on the grounds of their present excellent health.

A slightly different problem is raised by the demonstration of a local segmental lesion in the presence of recurrent attacks of generalized bronchitis or asthma. It is important to recognize that such local lesions are merely incidents in the course of a generalized disturbance and naturally would not benefit to the same extent by resection. Once again the history of "recent bronchitis" may be grossly misleading, since it may indicate, as we have previously noted, repeated infection in a region with bronchial damage or an actual recurrent acute generalized bronchitis. It may be possible to differentiate between these two groups only by a period of observation, during which actual incidents may be studied.

Treatment

The purpose of this work is to indicate a major source of bronchiectasis and to suggest that the attack on this disease be shifted to a much earlier stage in its natural history.

There are two principal factors to be considered in dealing with the pulmonary lesion. These are the infection and the mechanical aspects. The lesion may be large and yet there may be little or no clinical upset. In such cases the mechanical obstructive elements predominate. On the other hand, even small radiological lesions may be responsible for a considerable degree of general illness. Treatment must be directed against either or both of these factors.

Many of the cases when first seen with their initial illness present features so strongly resembling "pneumonia" that there may be a temptation to administer the modern antibiotics at once. However, when the laboratory findings and *x*-ray appearances are seen it is very often evident that the condition is not consistent with this diagnosis in its more classical sense. This is even more true if the patient be first seen a day or two after the usually short acute stage. We have found that so many have recovered rapidly without specific therapy that the value of antibiotics is often subject to doubt. We do not believe that the use of aureomycin or chloramphenicol is justifiable on the grounds of a possible virus basis for the infection (Robertson and Morle, 1951). Detailed serological investigations, while possibly of academic interest, should not be allowed to cloud the appreciation of the fundamental nature of these segmental lesions. On the whole, it has seemed reasonable to restrict the use of antibiotics to those cases in which the infective element predominates.

The basis for therapy should rest upon an attempt to reverse the sequence of events which have led to the develop-

ment of the segmental pulmonary lesion. It is essential that material which has been aspirated should be removed, thereby establishing adequate aeration of the involved segment and removing the element of collapse. In addition to this process of re-aeration, drainage will prevent stagnation within the segmental bronchi and diminish the likelihood of damage to the bronchial walls.

Properly conducted postural drainage should be instituted, having first established the exact site of the lesion. Drainage may be assisted in some cases by the use of steam inhalations or by short-wave diathermy, especially when the sputum is particularly tenacious. The actual procedure of bronchography has often been observed to increase the production of sputum, with consequent local improvement.

On the other hand, bronchoscopy is not likely to prove helpful, since the bronchial obstruction is usually peripheral and multiple. The bronchial secretions have been found to be so thick and tenacious as to block the suction tube. This suggests the need for an efficient liquefying agent which could be used endobronchially, but so far none appears to be forthcoming.

Expectorant mixtures seem to have little or no effect on these lesions, while the use of opiates is "the most frequently prescribed frustrator of the vital defence of the lungs" (Jackson, 1950).

Summary

A study of the clinical and radiological features of segmental aspiration pneumonia is presented.

There is bronchographic evidence of varying degrees of bronchial abnormality within such segmental lesions. It is shown that in some instances quite well-marked bronchiectasis can be demonstrated, and though this is usually reversible it is not always so. The possible position of this sequence of events in the natural history of bronchiectasis, together with rational preventive treatment, is discussed. It is believed that most recognized established bronchiectases originate from such segmental lesions.

Without the co-operation of the medical authorities of the Royal Air Force, and in particular Air Commodore Rumball, the consultant in medicine, this work would not have been possible. Dr. P. H. Whitaker and Dr. Robert Coope, whose clinical assistants we are, have given us every encouragement and placed the full facilities of their departments at our disposal. Our thanks are due to the radiography staff of the Liverpool Royal Infirmary and to Miss Smith for the *x*-ray photographs. We are also grateful for much material assistance from the University of Liverpool.

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It may surprise some that the rainfall last year over England and Wales exceeded by only 0.6 in. (1.5 cm.) the average value for the years 1881–1915. Yet such was the case, according to figures published in *The Times* this week by Dr. John Glasspoole. However, the year, in England and Wales, was drier than 1951 by 7.9 in. (20 cm.). Scotland and Northern Ireland experienced a rather drier year than average last year. The most remarkable meteorological event in 1952 was the 9 in. (22.9 cm.) of rain which fell at Longstone Barrow, four miles south of Lynmouth, during the 24 hours which began at 9 a.m. on August 15. This was the third largest daily measurement recorded in the British Isles.

INFLUENCE OF OESTRADIOL BENZOATE AND ORCHIDECTOMY ON THE RETICULO-ENDOTHELIAL SYSTEM

BY

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[WITH SPECIAL PLATE]

Oestrogens are used in the treatment of prostatic carcinoma and of cancer of the breast, urinary bladder, and other organs with good results, especially in the prostate. In the case of the prostate the beneficial action is accompanied by fibrosis (Fergusson and Pagel, 1945; Fergusson, 1948). Nicol and Helmy (1951) found that oestradiol benzoate, oestrone, stilboestrol, stilboestrol dipropionate, D.B.E. ($\alpha\alpha$-di-(*p*-ethoxyphenyl)-β-phenyl-bromo-ethylene), and dienoestrol stimulated the reticulo-endothelial system in the ovariectomized guinea-pig and suggested that the beneficial effect of oestrogenic treatment in cases of cancer of the prostate may be due to stimulation of the reticulo-endothelial system and the transformation of macrophages in the prostate into fibroblasts and fibrous tissue (Jaffé, 1938; Maximow and Bloom, 1948).

The part played by the reticulo-endothelial system in the defence against cancer has been referred to by several writers. Stern (1941) showed that the function of the system as tested by the Congo-red method was impaired in 86% of patients with malignant disease. Kavetzki and Diadjuscha (1937) showed that stimulation of the reticulo-endothelial system lowered the incidence of development of cancer metastases in rabbits inoculated intravenously with Browne-Pearce carcinoma, whereas blockade of the system raised the incidence of tumour growth. Diadjuscha (1937) has also shown that implantation of Ehrlich carcinoma into mouse liver or spleen or of Flexner–Jobling carcinoma into rat testes was invariably successful when the reticulo-endothelial system was blocked, and rarely so when it was stimulated.

Present Investigations

Our investigations were designed to study the effects of oestradiol benzoate, orchidectomy, and their combination on the activity of the reticulo-endothelial cells in the spleen, liver, lymph nodes, and prostate, and on the amount of fibrous tissue in the prostate. For this purpose 28 intact male guinea-pigs and 24 double-orchidectomized guinea-pigs were used. One month was allowed to elapse after orchidectomy to ensure complete recovery from the operation and disappearance of testicular hormone from the blood. All the animals received one daily subcutaneous injection of trypan blue at 4 p.m. for six days and were killed by chloroform the next day. The dosage of the dye was calculated on the basis of 0.8 ml. of a 1% solution in distilled water per 100 g. of body weight. Six of the intact animals and ten of the orchidectomized animals were given the dye only, and served as controls. The remainder were divided into groups in which each animal received one daily intramuscular injection of 0.5 mg. of oestradiol benzoate at 10 a.m. for one, two, three, or four weeks; these animals received the injections of dye during the last six days of the hormone treatment

and were killed the following day. Specimens of the prostate, spleen, liver, lymph nodes, bone marrow, skin and subcutaneous tissue, adrenal glands, and, when possible, the testes were fixed in Heidenhain's "susa" fluid. Sections were cut 10 microns thick and stained with dilute carbol-fuchsin or weak eosin. The activity of the reticulo-endothelial system was measured by the number of dye-bearing cells, and the intensity of the vital staining in the organs and tissues was examined.

Results

The results showed that in both the intact and the orchidectomized animals oestradiol benzoate produced hyperplasia and stimulation of the reticulo-endothelial macrophages, mainly in the spleen (Special Plate, Figs. 1, 2, and 3), liver, lymph nodes, and prostate, and that the degree of stimulation was roughly proportionate to the duration of the hormone treatment. In the orchidectomized animals the reticulo-endothelial system was more active, and oestradiol benzoate produced a greater response than in the intact animals.

In the spleen, prolonged oestrogenic stimulation appeared not only to produce a greater formation and activation of the reticulo-endothelial cells but also to assist their mobilization and liberation into the circulation. This was noted especially in the spleen of orchidectomized animals given the hormone for four weeks, in which the splenic sinuses were dilated and contained, in some animals, numerous dye-bearing cells, and in others a moderate number. In others the sinuses were practically empty (Fig. 4), although in the same animals the splenic vein and the intrahepatic branches of the portal vein contained a great number of dye-bearing cells. Furthermore, the peritoneal mesothelial cells covering the spleen became columnar and showed dye granules in the infranuclear zone as a result of the oestrogenic treatment, which confirms the findings recorded by Helmy and Nicol (1951) in female animals.

In the prostate, the dye-bearing cells appeared in the loose areolar tissue between the acini (Fig. 5). The vitally stained cells were very few in the intact animals not given hormone, but became numerous after oestrogenic treatment, and still more numerous when this was combined with orchidectomy. The thin layer of fibrous tissue which normally surrounds the prostatic acini became progressively thicker with hormone treatment, and the prostate showed the greatest degree of fibrosis in the orchidectomized animals which received oestradiol benzoate for four weeks (Fig. 6). Fibrosis was particularly marked in the region of the utriculus musculinus. The arrangement of cells around the prostatic acini in the hormone-treated animals suggests that oestradiol benzoate leads to the appearance of macrophages around the acini and that if the treatment is maintained these macrophages change into fibroblasts and fibrous tissue. Orchidectomy also seems to influence both the deposition of the macrophages and their transformation into fibroblasts. The macrophages in the prostate probably come mainly via the blood stream from the spleen and other reticulo-endothelial organs, where their mobilization is stimulated by the oestrogens, and partly from proliferation of pre-existing local cells having mesenchymal potencies.

Conclusions

The stimulating effect of orchidectomy on the reticulo-endothelial system may be explained by : (1) The absence of the neutralizing effect of androgens on oestrogens which are normally found in the male animal and are probably produced by the suprarenal glands. This neutralizing effect was shown by Ihrke and D'Amour (1931), Browman (1937), and Robson (1938). (2) The stimulating effect of orchidectomy on the anterior lobe of the pituitary, leading to the output of more adrenotropic hormone, which in turn leads to the production of more oestrogens by the suprarenals.

The results of the present investigations, therefore, show that oestrogens and orchidectomy both stimulate the reticulo-endothelial system and in this manner probably increase the general resistance against cancer; that in the prostate they induce the appearance of macrophages and later of fibrous tissue, which acts as a local defence against the spread of cancer; and that oestrogenic treatment combined with orchidectomy produces a more intense result than either alone.

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RESPONSE IN DOGS TO RELAXANTS DERIVED FROM SUCCINIC ACID AND CHOLINE

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It has recently been reported (Hall, 1952) that suxethonium is a useful relaxant in operations on dogs, and as such is a welcome addition to the surgical practice concerned with this species. There was, however, a difference between the effects of the drug in dogs and in man, dogs being more sensitive and responding with longer apnoea to smaller doses. In an investigation on succinylcholine sensitivity in man (Evans, Gray, Lehmann, and Silk, 1952) a correlation had been found between low pseudo-cholinesterase level in the plasma and prolonged response to succinylcholine. This observation, and experiments *in vitro*, suggested that in man the drugs produced depolarization, not only directly but also by inhibiting the true cholinesterase, thus raising the acetylcholine concentration in the neuromuscular end-plates, and that the short duration of this effect was due to the rapid hydrolysis of succinylcholine by the pseudo-cholinesterase of the plasma. We therefore decided to investigate the enhanced effect of suxethonium in dogs along these lines by finding out whether there were differences between the enzyme systems of man and dog.

Methods

All observations in dogs except one were made in the course of necessary treatment. "Brevidil E," which used to be suxethonium di-iodide and is now obtainable commercially as the dibromide, and "scoline" (suxamethonium chloride), which is succinylcholine dichloride, were both used *in vivo* and *in vitro*. There was no major difference in their behaviour. All doses used *in vivo* and *in vitro* are expressed in terms of the active cation. The *in vitro* techniques followed were the same as described previously (Evans *et al.*, 1952). They depend on the evolution of CO_2 from bicarbonate buffer by the products of ester hydrolysis; the activity

of the enzymes is expressed as μl. of CO_2 formed per minute by 1 ml. of serum or packed red cells at 37° C. (see McArdle, 1940).

Results

In 25 operations on dogs suxethonium was given in dosages mostly from 0.08 to 0.15 mg. per lb. body weight; in some instances the amounts administered were even less. To man four to six times these dosages are administered, yet the apnoea produced in dogs was longer than that seen normally in man. It has to be conceded that in the chest conditions hyperventilation may have played a part in extending the duration of apnoea.

We then established that in dogs, as in man, succinylcholine and suxethonium inhibit the hydrolysis of acetylcholine both by the true cholinesterase prepared from red cells and by the pseudo-cholinesterase of the plasma, and, furthermore, that succinylcholine and suxethonium themselves are hydrolysed by pseudo-cholinesterase and not by the red-cell enzyme (for details see Table I). The inhibition of acetylcholine breakdown by dog's serum in the presence of succinylcholine had already been shown by Bovet and his colleagues (1951).

TABLE I.—*Succinylcholine and Suxethonium in Dogs' Blood. Breakdown by Pseudo-cholinesterase, Inhibition of Acetylcholine Breakdown by Both Pseudo-cholinesterase and True Cholinesterase*

Substrate (Active Cation)	μl. CO_2 Liberated by 1 ml. Serum or Packed Red Cells per Minute at 37° C.				
	Acetylcholine	Succinylcholine	Suxethonium	Acetylcholine + Succinylcholine	Acetylcholine + Suxethonium
Pseudo-cholinesterase of serum:					
Acetylcholine: 6·5 mg./ml. ..	68	2	—	14	—
Succinylcholine: 13 mg./ml. ..	43	4	—	20	—
Suxethonium: 14 mg./ml. ..	45	7	2	17	8
True cholinesterase of red cells:					
Acetylcholine: 0·65 mg./ml. ..	18	—	—	1	—
Succinylcholine: 1·3 mg./ml ..	16	—	—	2	—
Suxethonium: 1·4 mg./ml. ..	18	—	—	2	0

In man the cause of prolonged apnoea after succinylcholine had been a low activity of the pseudo-cholinesterase of the plasma. We therefore thought at first that dogs might normally have a much lower pseudo-cholinesterase in their plasma than man. Table II shows that, although the values for pseudo-cholinesterase tend to be lower in dog than in man, in whom the normal range is 55 to 120 units, only one dog had an esterase value below 40, which might in man cause a significantly prolonged apnoeic response to succinylcholine. However, there was a considerable difference between the level of true cholinesterase of the red cells in man and dog. The values for man are about 80 to 120 (although very occasionally they may be as low as 60 to 80); and it will be seen in Table II that we found them to be six to eight times lower in dogs.

As pointed out in the introduction to this paper, the action of succinylcholine in man can be visualized as a combination of it with the two cholinesterases. True cholinesterase + succinylcholine causes the pharmacological effect, and pseudo-cholinesterase + succinylcholine brings it to its rapid end. The duration of apnoea would then depend on the dosage of succinylcholine given and on the concentration of the two esterases combining with it—that is, equilibria will be established between the free succinylcholine and the succinylcholine adsorbed both on the true cholinesterase on the one hand and on the pseudo-cholinesterase on the other. Of these the combination pseudo-cholinesterase + succinylcholine is unstable and results in hydrolysis of the adsorbed drug. This will free pseudo-cholinesterase, which will thus become available for the remaining free succinylcholine. As the free drug is also in equilibrium with that combined with the true cholinesterase a fall in its concentration will result in a release of succinylcholine from that combination and the pharmacological effect will progressively abate.

TABLE II.—*Levels of Pseudo-cholinesterase (Serum) and True Cholinesterases (Red Cells) in Dogs' Blood. None of the Dogs Suffered from Anaemia or Liver Disease*

Animal	μl. CO_2 Liberated per ml. Serum or Packed Red Cells per Minute at 37° C.	
	Pseudo-cholinesterase (6·5 mg. Acetylcholine/ml.)	True Cholinesterase (0·65 mg. Acetylcholine/ml.)
Greyhound ..	66	15
Mongrel ..	66	10
Mongrel ..	86	9
Cairn ..	55	14
Greyhound ..	68	18
Dachshund ..	49	9
Alsatian ..	65	13
Puppy ..	50	20
Mongrel ..	43	16
Mongrel ..	75	16
Labrador ..	33	21
Labrador ..	49	19

The difference between the action of succinylcholine or suxethonium in man and dog can be explained on the basis of these equilibria. With a low concentration of true cholinesterase less free succinylcholine or suxethonium is required for the inhibitory combination which produces subsequent depolarization, and, although the destruction by pseudo-cholinesterase is almost as efficient as in man, the drain on the remaining free choline derivative cannot have the same effect because in the dog lower concentrations would still suffice to occupy the smaller amount of true

TABLE III

Type of Dog and Sex:	Mongrel, Male	Mongrel, Female	Labrador, Male	Labrador, Male
Age and weight ..	2 years; 25 lb. (11·3 kg.)	12 years; 22½ lb. (10·2 kg.)	6 months; 41 lb. (18·6 kg.)	3½ years; 63 lb. (28·6 kg.)
Premedication ..	Pethidine, 25 mg.; scopolamine, 1/200 gr.	Pethidine, 15 mg.; scopolamine, 1/200 gr.	Pethidine, 50 mg.; scopolamine, 1/200 gr.	Pethidine, 200 mg.; scopolamine, 1/100 gr.
Thiopentone (g.) ..	0·3	0·3	0·45	0·6
Maintenance ..	N_2O/O_2, 50:50	N_2O/O_2, 50:50	N_2O/O_2, 50:50; thiopentone, q.s.	N_2O/O_2, 50:50; minimal trilene; thiopentone, q.s.
Pseudo-cholinesterase in plasma (units) ..	43	75	33	49
True cholinesterase in red cells (units) ..	16	16	21	19
Succinylcholine (mg.) (active cation) ..	2·5	2·2	5	7
Duration of apnoea (min.)	14	12	15	13
Thiopentone (g.)	0·05	—	—	—
Succinylcholine (mg.)	2·5	2·2	—	—
Duration of apnoea (min.)	18	13	—	—
Pseudo-cholinesterase injected (units) ..	21,000	21,000	21,000	21,000
,, in plasma (units) ..	102	111	54	63
True cholinesterase in red cells (units) ..	—	15	18	16
Thiopentone (g.)	0·1	0·05	0·05	0·1
Succinylcholine (mg.)	2·5	2·2	5	7
Duration of apnoea (min.)	4	*No apnoea**	4·5	*No apnoea**
Succinylcholine (mg.)	—	—	5	—
Duration of apnoea (min.)	—	—	5	—

* Though there was no apnoea there was shallow breathing, needing some assisted respiration in dog 2.

cholinesterase available. However, it should be possible to increase the pseudo-cholinesterase of the plasma in the dog and thus to lower the concentration of free succinylcholine or suxethonium so rapidly that even the low concentration of the drug required for inhibition of the true cholinesterase in that animal will be effectively attacked. We therefore injected a highly concentrated solution of pseudo-cholinesterase intravenously into four dogs in the course of operations for mastectomy or conditions requiring orthopaedic treatment, and compared the effect of equal amounts of suxethonium given before and after the pseudo-cholinesterase level of the plasma had been increased.

As will be seen in Table III, after the pseudo-cholinesterase had been effectively raised succinylcholine was as short-acting in dog as it is known to be in man. To exclude the effects of premedication and the possibility that apnoea was due to artificial hyperventilation, one experiment was performed in which only thiopentone was used for induction and no artificial respiration was given during apnoea beyond one inflation per minute. Table IV shows that the

TABLE IV.—*Adult Mongrel Bitch, Weight 31 lb. (14 kg.)*

0	min.	0·5 g.	thiopentone Recording apparatus for blood pressure and respiratory rate connected
18	,,	0·1 g.	thiopentone Pseudo-cholinesterase, 46; true cholinesterase, 18
23	,,	3·5 mg.	suxethonium: 16 min. apnoea
43	,,	0·1 g.	thiopentone
48	,,	3·5 mg.	suxethonium: 11 min. apnoea
70	,,	2 mg.	succinylcholine: 5 min. apnoea
83	,,	0·1 g.	thiopentone
93	,,		injection of 21,000 units pseudo-cholinesterase
97	,,		Pseudo-cholinesterase, 76; true cholinesterase, 15·5
102	,,	3·5 mg.	suxethonium: no apnoea, 3 min. respiratory depression
112	,,	3·5 mg.	suxethonium: no apnoea, 4 min. respiratory depression
122	,,	2 mg.	succinylcholine: no apnoea, 2 min. respiratory depression
130	,,		Pseudo-cholinesterase, 78; true cholinesterase, 15

raising of the pseudo-cholinesterase level was effective under these conditions. Blood-pressure readings were obtained throughout and allowed an exclusion of asphyxia. Both brevidil E and scoline were used and noted as such in terms of active cation.

Discussion

Our findings support the suggestion that the effect of succinylcholine and suxethonium is the outcome of an interplay between these compounds and the two cholinesterases. The fact that the dog is much more sensitive than man would then be explained by the finding of a six to eight times lower true cholinesterase concentration in the red cells. Similarly, the fact that the sensitivity of the dog can be lowered to levels seen in man by raising the pseudo-cholinesterase level of the plasma can be understood on the bases of these considerations. We have assumed that the two esterases in man and dog are the same enzymes, and that the differences in activity of blood and plasma are due to different enzyme concentrations. It is, of course, possible that there are species variations and that the affinities rather than the concentrations are different. However, the interplay between compounds and enzymes would have the same outcome whether the enzymes differ in concentration or in affinity. Apart from theories, our findings have two practical consequences: the absence of side-reactions in the dog when given human cholinesterase preparations justifies its trial in man in cases of succinylcholine sensitivity. The use of the enzyme will be of advantage in veterinary medicine, as it will convert succinylcholine and suxethonium from comparatively long-time relaxants into compounds acting for a few minutes only, thus bringing into the surgery of the dog the advantages found in the use of succinylcholine and suxethonium in man.

Summary

Dogs are more sensitive to suxethonium and succinylcholine than man. When injected with doses about one-fifth of those used in man they react with an apnoea of about five times longer duration.

The pseudo-cholinesterase concentration in dogs' serum is not much lower than that in man, but the true-cholinesterase concentration in the red cells is only about one-seventh. It is suggested that there is a correlation between higher sensitivity and lower true cholinesterase and that raising or lowering any of the two enzymes will raise or lower the time of apnoea after succinylcholine or suxethonium.

In five dogs raising of the pseudo-cholinesterase level in the circulating plasma shortened effectively the time of apnoea after suxethonium or succinylcholine. The theoretical and practical significance of these findings is discussed.

We should like to express our thanks to Dr. E. B. McLean, of the U.S.A., who provided us with a pseudo-cholinesterase preparation containing 21,000 units per ml. This solution will in due course become available commercially under the name of "cholase."

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EFFECT OF PSEUDO-CHOLINESTERASE LEVEL ON ACTION OF SUCCINYLCHOLINE IN MAN

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Human blood contains two cholinesterases. One is found in the plasma, and is unspecific so far as acetylcholine is concerned; it is therefore called pseudo-cholinesterase (Ps.ChE.). The other is the true cholinesterase of the red cells (Tr.ChE.). When succinylcholine was rediscovered by Bovet, Bovet-Nitti, Guarino, Longo, and Marotta (1949) and recommended as a muscle relaxant, its short action was already ascribed to its enzymatic destruction by the blood (Bovet-Nitti, 1949); this work was done on rabbits. Evans, Gray, Lehmann, and Silk (1952a) showed that, in man, of the two enzymes the pseudo-cholinesterase was responsible for the hydrolysis of succinylcholine. Bourne, Collier, and Somers (1952) found a significant difference in the pseudo-cholinesterase level when they compared six patients who had recovered normally from the effect of succinylcholine with six others whose response lasted beyond eight minutes. Evans *et al.* (1952a) demonstrated an inverse relationship between the duration of apnoea and the pseudo-cholinesterase level in the serum. It was suggested that unduly prolonged response to the drug should be treated with

transfusion of whole blood, which even on storage contains some 30 units of pseudo-cholinesterase per ml. of plasma. We were then offered for therapeutic trial a concentrated solution of human pseudo-cholinesterase by Dr. McLean, of the U.S.A., and this preparation was first used in dogs, in whom it was found by Hall, Lehmann, and Silk (1953) to be highly efficaceous in the reversal of apnoea following injection of succinylcholine. Encouraged by these results, we injected the enzyme preparation, which will become available commercially as "cholase," in one of us (P. W. S. G.) and, following this, into patients. Cholase is prepared by ethanol fractionation and is a subfraction of Cohn's globulin fraction IV-6 (Surgenor, 1949).

Material and Methods

The levels of pseudo-cholinesterase and true cholinesterase were measured in serum and in laked and washed red cells respectively by the manometric method as described by McArdle (1940). This technique measures the CO_2 liberated from a bicarbonate buffer by the products of ester hydrolysis, and the activity of the enzyme solutions as expressed as μl. of CO_2 formed per minute by 1 ml. of serum or packed red cells at 37° C. The pseudo-cholinesterase was measured, using serum in a final dilution of 1 in 15 with 8 mg. of acetylcholine chloride per ml. as substrate; the true cholinesterase was determined with the final 1 in 75 dilution of packed, washed, and laked red cells with 0.8 mg. of acetylcholine chloride as substrate. Cholase activity was measured in final dilutions of 1 in 1,500.

Experimental Procedure.—Four patients were given thiopentone for induction of anaesthesia. A blood sample was taken for measurement of the cholinesterases. When breathing was regular and no effect on it by thiopentone was noticeable, succinylcholine was injected and the time of apnoea was measured with a stop-watch. When breathing was fully re-established renewed thiopentone had to be given in one case (No. 1), but in the others the induced sleep was still deep enough to make this unnecessary. Cholase was then injected intravenously, and after 90 seconds a second blood sample was taken for measurement of the enzyme levels. Succinylcholine was then again injected as before and the resulting apnoea was measured with a stop-watch. The whole experiment lasted less than 20 minutes in all four cases.

Results

Case 1.—Man aged 61, weight 11 st. 4 lb. (71.7 kg.). Induction, 0.5 g. thiopentone. Blood enzyme levels: Ps.ChE., 90 units; Tr.ChE., 138 units. 50 mg. succinylcholine chloride injected; *apnoea of 130 seconds* followed. On waking up, 0.5 g. thiopentone given. 12 ml. pseudo-cholinesterase (252,000 units) injected. Blood enzyme levels: Ps.ChE., 183 units; Tr.ChE., 149 units. 50 mg. succinylcholine chloride injected; *apnoea of 66 seconds* followed. Blood enzyme levels: 2 hours later: Ps.ChE., 185 units; Tr.ChE., 152 units. 18 hours later; Ps.ChE., 125 units; Tr.ChE., 149 units. 24 hours later: Ps.ChE., 129 units; Tr.ChE., 132 units.

Case 2.—Man aged 52, weight 14 st. (88.9 kg.). Induction, 0.5 g. thiopentone. Blood enzyme levels: Ps.ChE., 72 units; Tr.ChE., 124 units. 50 mg. succinylcholine chloride injected; *apnoea of 210 seconds* followed. When breathing was fully re-established 5 ml. pseudo-cholinesterase (105,000 units) was injected. Blood enzyme levels: Ps.ChE., 95 units; Tr.ChE., 129 units. 50 mg. succinylcholine chloride injected; *apnoea of 110 seconds* followed. Blood enzyme levels:—3 hours later: Ps.ChE., 86 units; Tr.ChE., 120 units. 24 hours later: Ps.ChE., 74 units; Tr.ChE., 131 units.

Case 3.—Woman aged 67, weight 8 st. 11 lb. (55.8 kg.). Induction, 0.5 g. thiopentone. Blood enzyme levels: Ps.ChE., 34 units; Tr.ChE., 99 units. 75 mg. succinylcholine chloride injected; *apnoea of 375 seconds* followed. When breathing was fully re-established 6 ml. pseudo-cholinesterase (126,000 units) was injected. Blood enzyme levels: Ps.ChE., 73 units; Tr.ChE., 97 units. 75 mg. succinylcholine chloride injected; *apnoea of 135 seconds* followed.

Case 4.—Woman aged 63, weight 12 st. 4 lb. (78 kg.). Induction, 0.45 g. thiopentone. Blood enzyme levels: Ps.ChE., 23 units; Tr.ChE., —. 50 mg. succinylcholine chloride injected; *apnoea of 555 seconds* followed. When breathing was fully re-established 3 ml. pseudo-cholinesterase (63,000 units) was injected. Blood enzyme levels: Ps.ChE., 36 units; Tr.ChE., —. 50 mg. succinylcholine chloride injected; *apnoea of 345 seconds* followed.

Table I summarizes the pseudo-cholinesterase levels before and after pseudo-cholinesterase injection and the time of apnoea before and after the raising of the enzyme level.

TABLE I.—*Pseudo-cholinesterase Level and Effect of Succinylcholine Before and After Injection of Cholase*

Case No.	Pseudo-cholinesterase (Units)		Apnoea following Succinylcholine (Seconds)	
	Before Cholase	After Cholase	Before Cholase	After Cholase
1	90	183	130	66
2	72	95	210	110
3	34	73	375	135
4	23	36	555	345

It will be noted that the levels rise rather less than they would have done if all the pseudo-cholinesterase had remained in the blood stream. Table II shows the "leakage into the tissues." There was, as would be expected, more deficit in the person weighing 14 st. (88.9 kg.) (Case 2) than

TABLE II.—*Injection of Pseudo-cholinesterase and Rise in Enzyme Level of Serum*

Case No.	Total Units Enzyme Injected	Rise in Units per ml. Serum	Expected Rise (Plasma Volume taken to be 2,500 ml.)	Units not Recovered per ml. Serum
1	252,000	93	100	7
2	105,000	23	42	19
3	126,000	39	50	11
4	63,000	13	25	12

in the others, who weighed much less. This deposition of additional enzyme in the tissues must have led to destruction of succinylcholine in these tissues and lowered the factor of 200, which usually results when the units of pseudo-cholinesterase are multiplied by the minutes of apnoea following administration of 30–50 mg. of succinylcholine to an adult (Evans *et al.*, 1952a). Table III shows that this

TABLE III.—*If Succinylcholine Chloride is Injected Into an Adult at a Dosage of 30–50 mg. the Resulting Apnoea Depends on the Pseudo-cholinesterase Level of the Serum: Pseudo-cholinesterase in Units × Apnoea in Minutes = 200*

Case No.	Fall of (Enzyme Units × Minutes Apnoea) Factor on Injection of Cholase	
	Factor before Injection of Cholase	Factor after Injection of Cholase
1	213	208
2	213	165
3	252	166
4	198	143

relationship applied well in the cases to begin with, but that the factor was lowered after cholase injection, with the exception of Case 1, in which, in view of the large amount of enzyme injected, the leakage into the tissues was relatively insignificant when compared with the rise in the plasma level.

Cases 3 and 4 received blood transfusions during the operation, but Cases 1 and 2 could be followed up for one day, and it was notable that there was still a significantly increased pseudo-cholinesterase level after 24 hours, when

252,000 units had been injected, but not after 105,000 units. Thus it may be possible to protect a person by the prior injection of pseudo-cholinesterase, but to obtain a prolonged protection the dosages will have to be large. In none of the patients did we discover any excretion of pseudo-cholinesterase in the urine.

We have elsewhere dealt with the suggestion that thiopentone was the true causative agent in increased sensitivity to succinylcholine (Evans, Gray, Lehmann, and Silk, 1952b); it will be noted that, at least in Case 1, thiopentone was injected before the succinylcholine was given, with and without cholase; the difference in the duration of apnoea can therefore not have been connected with thiopentone. Hall, Lehmann, and Silk (1953) also paid particular attention to this point in their work on dogs, and have excluded apnoea due to thiopentone or to artificial respiration in the animals. We performed a special test on one of us (P. W. S. G.), in whom we injected succinylcholine without prior thiopentone. We have referred to this briefly before (Evans *et al.*, 1952b); here are the details of this experiment:

Man aged 30, weight 15 st. (95.3 kg.). Blood enzyme levels: Ps.ChE., 82 units; Tr.ChE., 136 units. 10 mg. succinylcholine chloride injected; *apnoea of 40 seconds* followed. One week later: Blood enzyme levels: Ps.ChE., 95 units; Tr.ChE., 129 units. 3 ml. pseudo-cholinesterase (63,000 units) injected. Blood enzyme levels: Ps.ChE. 122 units; Tr.ChE., 123 units. 10 mg. succinylcholine chloride injected; this was followed by *no apnoea*.

Since our last publication dealing with two patients (Evans *et al.*, 1952a) we have seen more cases in which a prolonged effect of succinylcholine could be explained by the finding of a low pseudo-cholinesterase level in the serum. There were, however, two patients in whom the enzyme level was normal; both were suffering from cancer and inanition, and had altered electrolyte values in the serum—particularly a low serum potassium. It is conceivable that in such patients a paralysis of muscles will not be easily reversed, because of a loss of excitability. Recently nikethamide was recommended as an antidote against succinylcholine (Barron, 1952); it is possible that it was of use in this type of case. Nikethamide has not been seen by us to lower the response to succinylcholine in man *in vivo* or to have an effect on either true cholinesterase or pseudo-cholinesterase *in vitro*.

Summary

The injection of pseudo-cholinesterase shortens the apnoeic response to succinylcholine. Not all the pseudo-cholinesterase injected can be recovered in the plasma; 20,000–50,000 units are "leaking" into the tissues within a few minutes. In one patient who received 252,000 units (equivalent to about 2.5 litres of plasma) the serum enzyme level was still raised after 24 hours, but no enzyme was found in the urine.

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The history of King Edward VII's Hospital for Officers is the subject of an interesting booklet recently published. The hospital was founded by Miss Agnes Keyser ("Sister Agnes") during the Boer War. King Edward, a personal friend of Miss Keyser, fulfilled the last social engagement of his life at the hospital, of which he was patron. The booklet (price 2s. 6d.) is obtainable from the hospital, now at Beaumont Street, London, W.1, and proceeds from its sale will be devoted to the funds of the hospital.

BREAST-FEEDING IN THE OXFORD CHILD HEALTH SURVEY

PART I—A STUDY OF MATERNAL FACTORS

BY

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The present investigation relates to 574 mothers* who regularly attended the Oxford Child Health Survey for at least a year. Its purpose is to compare the circumstances of mothers who failed to establish or maintain lactation with those who succeeded in feeding their babies for several months. It will shortly be followed by a descriptive account of the effect on the babies of breast- as opposed to bottle-feeding.

Prevalence of Breast-feeding

None of the mothers failed to put their babies to the breast at least once, but lactation had ceased in 88 within four weeks of delivery, and a further 82 had weaned their babies before the age of 4 months. At the opposite end of the scale there were 70 mothers who gave their babies nothing but breast milk for six months or longer, and 53 who were still giving their babies some breast milk after the age of 10 months. The mean duration of complete breast-feeding was 5.3 months (± 3.62) and of partial breast-feeding (weaning period) 3.7 months (± 1.90).

There was a general tendency for mothers who weaned their babies early to do so quickly, and for mothers who weaned them late to do so slowly. Thus half the babies breast-fed for more than six months had a weaning period which exceeded twelve weeks, whereas nearly two-thirds of the babies who were given bottle feeds within four weeks of birth were completely weaned in less than three weeks.

Compared with recent surveys in this country, the prevalence of breast-feeding is high (see Bibliography). In view of the method of recruiting into the Child Health Survey (Stewart and Russell, 1952) this is unlikely to be a characteristic of all Oxford mothers.

Factors Associated with Breast-feeding Habits

In the following account three groups of mothers will be distinguished: (1) those who did not begin weaning until their babies were over 4 months old (53.8%); (2) those who maintained complete breast-feeding for more than three weeks but less than four months (30%); and (3) those in whom lactation was never firmly established (16.2%).

Age and Parity

In the National Survey of all babies born in England and Wales during the week March 3–9, 1946 (Royal College of Obstetricians and Gynaecologists, 1948) it was found that, after standardizing for social class and parity, there was no consistent relationship between the age of the mother and the duration of breast-feeding, but first babies were breast-fed longer than other babies. Hughes (1942, 1948), and Dummer (1949) also found that the incidence of breast-feeding was higher among primiparae, but Norval (1947) and Dykes (1949, 1950) found no relationship between breast-feeding and parity, and Neale *et al.* (1943) thought that first-born babies had less breast milk than other babies.

In the present investigation there were 264 primiparae, of whom 111 were under 25 years and 20 over 34 years. In these two age groups 11% and 25% respectively failed to

*There are 580 babies in the Survey Group, but five were adopted and two were twins.

establish breast-feeding, and 42% and 35% maintained it for more than four months. The corresponding figures for primiparae of intermediate age were 9% and 65%.

For multiparae there was no distinction by age, but mothers with two or three children more often maintained lactation for over four months (59%) than either primiparae (53%) or mothers with four or more children (45%), though these differences only reach the 5% level of significance. When both parity and social class (Registrar General, 1938) were taken into consideration two distinctly different trends were revealed. For mothers in social classes I and II the incidence of prolonged breast-feeding increased steadily with increasing size of family; but in all other classes mothers with two or three children had a higher incidence than either mothers with first babies or mothers with four or more children. Despite previous observations to the contrary, there seemed to be no association between spacing of children and breast-feeding habits, but this may be due to the fact that only 30 mothers had produced two babies within a year.

To sum up, the observed relationships between breast-feeding habits, age, social class, and parity suggest that previous experience of maternity has a favourable effect on lactation, but that this is not enough to offset the adverse effects of heavy domestic commitments and a low wage packet.

Physique and Health

Breast-feeding habits were found to bear no relationship to the height or weight of the mothers, or to a combined assessment of physique based on the height/weight ratio ($Ht\sqrt[3]{Wt.}$). There was, however, a close association between health and lactation. Thus, 58% of mothers whose health was uniformly good after delivery breast-fed their babies for more than four months and only 14% failed to establish lactation. The corresponding figures for mothers whose post-natal health was poor are 38% and 24% respectively. These differences reach the 1% level of significance. No definite relationship between health and social class could be established, but there was a definite tendency for health to deteriorate with age and with succeeding pregnancies.

Social and Economic Circumstances

The relationship between social class and breast-feeding has been variously interpreted in different parts of the country. In the National Survey there appeared to be a distinct social gradient, mothers in the professional and administrative classes being more successful in establishing and maintaining breast-feeding than working-class mothers. Gordon (1942) at Ilford and Ross and Herdan (1951) at Bristol found the same tendency, but Robinson in Liverpool, Dummer in Hitchin, and Dykes in Luton found no consistent association between social class and lactation.

In the present survey 66% of the mothers in social classes I and II completely breast-fed their babies for more than four months, compared with 54% in social class III and 44% in social classes IV and V. The same trend was observed in respect of the period of partial breast-feeding, but in social classes IV and V a disproportionately large number of mothers continued to feed their babies for more than nine months. This tendency for a low general prevalence of breast-feeding to be associated with a high late prevalence is apt to cause confusion when comparing the breast-feeding habits of different groups of mothers.

As it was possible that an occupational classification no longer provided a reliable index of material prosperity, an alternative "amenities rating" was applied to the survey mothers (Stewart and Russell, 1952). The object of this was to distinguish mothers who enjoyed the best opportunities for child-bearing from those whose commitments or lack of facilities handicapped them in any way. The rating was based solely on objective criteria and took into consideration such things as the structural repair of the house, the water, sanitary and cooking arrangements, garden facilities, the number of persons per room, the presence of other young children, lodgers, "in-laws," paid helpers, etc. According to this index, 20% of the mothers were favourably situated, and 56% moderately and 24% severely handicapped. The corresponding proportions for prolonged breast-feeding were 64%, 54%, and 43%, differences which are significant at the 1% level.

The individual components of the amenities rating appear to have a cumulative effect. Thus, the relationships between household density—that is, persons per room—and lactation, and between outsiders in the home and lactation, were of the same order but of doubtful significance; but no direct association between the duration of breast-feeding and the presence or absence of a paid domestic helper could be demonstrated. There was little to distinguish mothers who shared the house with "in-laws," mothers who took in lodgers to make ends meet, and mothers who were themselves lodgers in someone else's house; but compared with mothers who had a house to themselves the overall incidence of breast-feeding was low in all three groups.

Wages and housekeeping allowances were not incorporated in the amenities rating, since no figures were available for one-fifth of the mothers; but within the group which was assessed there seemed to be no consistent relationship between the amount of money spent on food and breast-feeding habits.

Only 38 mothers resumed gainful employment before the babies were 4 months old. In this small group the incidence of breast-feeding was exceptionally low, but how many of these mothers deliberately stopped feeding their babies and how many would not have continued in any case is not known. There were eleven unmarried mothers, five of whom continued to breast-feed their babies for over four months.

Maternal Efficiency

Marks were awarded for maternal efficiency on the basis of a number of subjective assessments concerning the appearance of the house and the child on three home visits made during the first year (Thwaites and Sutherland, 1952): 64% of the mothers scored 12 (full marks), 27.6% scored between 11 and 9, and 8.4% scored fewer than 9 marks. The corresponding proportions for prolonged breast-feeding were 61.1, 51.2, and 24.5%.

Since maternal efficiency is correlated not only with social class but also with health, parity, and the amenities rating, it is difficult to assess the significance of its association with breast-feeding. Taken at its face value, the relationship suggests that mothers who are good housekeepers have less difficulty in establishing and maintaining breast-feeding than mothers who are always at "sixes and sevens." But whether this is a direct effect or merely due to the fact that "efficiency" is one of the ways in which health, education, income, and appropriate facilities manifest themselves it is impossible to say. Within the group with top marks for maternal efficiency were 47 mothers from social classes I and II who also attended a private mothercraft clinic. No fewer than 35 of these (approximately 75%) maintained full lactation for at least four months. In this clinic great stress is laid on the importance of breast-feeding; small complementary feeds are encouraged until lactation is established, and a long weaning period is advised.

Mode, Place, and Time of Delivery

Less than half the survey babies were born at home. The hospital and nursing-home deliveries included 34 forceps deliveries and 7 caesarean sections; but in spite of this the group as a whole had a relatively high incidence of prolonged breast-feeding (56%). Further analysis of the institutional deliveries showed that the mothers in social classes I and II represented a typical cross-section of the whole survey group in respect of "general health" and "obstetrical emergencies," but the mothers in social classes IV and V included an exceptionally large number of abnormalities under both headings. Both subgroups were mainly composed of primiparae. When the corresponding rates for prolonged breast-feeding were inspected it was found that only 39% of the mothers in social classes IV and V breast-

fed their babies for four months, compared with 68% in social classes I and II. For mothers who were confined at home the overall incidence of prolonged breast-feeding was 50% with no variation in the different social classes.

The babies who were born in the winter and spring (December to May inclusive) were breast-fed longer than babies born in the summer or autumn, but the difference is of doubtful significance ($P<0.20$). Neither sex nor birth weight appeared to influence breast-feeding habits.

Discussion

So interwoven are the factors which influence breast-feeding habits that it is not only impossible to assess their individual contribution but even difficult to distinguish favourable and unfavourable influences. It is, for instance, unlikely that previous experience of child-bearing has anything but a beneficial effect on lactation, but it is not until parity and economic status are separated from one another that the true physiological effect is seen.

The present investigation has shown that mothers with heavy domestic commitments and lack of suitable facilities tend to wean their babies early, but we are still no nearer knowing what in "the complex of adverse circumstances which accompany poverty" (Ryle, 1946) has the most harmful effect. Other observers have failed to establish a direct relationship between lactation and nutrition (Robinson, 1939). It is improbable, therefore, that the observed association is due to malnutrition. It could, however, be due merely to the fact that the commercial advertising of baby foods is more successful in working-class than in professional circles. Once established, breast-feeding is both simpler and cheaper than artificial feeding. It is therefore unlikely that a working-class mother with several children weans her baby merely to "save trouble." On the other hand, breast-feeding can be very tedious in the early days and, other things being equal, a mother with heavy commitments and inadequate assistance is less likely to be successful in establishing lactation than a mother who can devote more time and attention to the new baby.

The relatively high level of breast-feeding among mothers delivered in hospital could be due to a bias in favour of hospitals by mothers who are otherwise favourably situated to establish and maintain lactation, or to the setting itself, which is, domestically speaking, restful and one in which good habits could be encouraged not only by precept, but also by example. It has certainly been a feature of other investigations (Hughes, 1948 ; Dummer, 1949 ; Dykes, 1950 ; Royal College of Obstetricians and Gynaecologists, 1948), but the relative importance of temporary freedom from worry, "selective recruitment," and example has not yet been measured.

Enough has been said to show how difficult it is to disentangle even the few factors chosen for special study, and how impossible to arrive at firm conclusions. With the small numbers available, the survey data have done little more than confirm the observations of previous writers and provide a background for the survey children. It may, however, be possible for larger clinics to select one or two of the more promising lines of inquiry for closer study. Meanwhile, the relatively high incidence of prolonged breast-feeding in the group as a whole suggests that a target of "breast-feeding by 80% of mothers for six months [which] would materially reduce both morbidity and mortality rates in infancy . . . is perhaps more readily obtainable than is generally believed" (Cruickshank, 1945).

Summary

Among 574 mothers attending the Oxford Child Health Survey, 53.8% breast-fed their babies completely for over four months and 16.2% for less than three weeks.

Social and economic conditions have a pronounced effect on breast-feeding habits. If they are good the incidence of prolonged breast-feeding increases with the increasing size of the family ; if not it will diminish.

The high prevalence of breast-feeding among mothers delivered in hospital emphasizes the importance of freedom from domestic commitments in the early days of lactation.

I am indebted to Sister Wood, of the Oxford Mothercraft Clinic; to my colleagues in the Child Health Survey, particularly to Miss Thwaites, until recently our social worker; and to Dr. Alice Stewart for her encouragement and help. The Medical Research Council contributed towards the expenses of this investigation.

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Medical Memoranda

Cholangiography by Means of a Barium Enema

The inflamed gall-bladder containing stones not infrequently becomes attached to a neighbouring hollow viscus, and on occasion a stone or stones may ulcerate into the intestinal tract, either completing the passage safely or producing intestinal obstruction, the complication of obstruction being more likely when the fistula is between the gall-bladder and duodenum.

Examples of the spontaneous passage of gall-stones by the intestinal route were commonplace when biliary surgery was a rarity. The following case is worth recording because the safe passage of the stone or stones did not result in the fistula closing, owing to the normal channel being blocked by a stone in the ampulla of Vater. Moreover, the patient's symptoms were presumably due to the persistence of the fistula, and the presence of this fistula was demonstrated radiologically before operation.

CASE REPORT

The patient, a married woman aged 70, was referred to me by Dr. Russell Fraser. She had been a known diabetic since 1939. In 1947 she suffered from severe diarrhoea for about nine months, and this cleared up after a single injection of liver extract. Up to three months previously she remained well so far as her gastro-intestinal system was concerned, and then the diarrhoea recurred. The bowels were opened 10 to 12 times daily, and she was most affected at night and in the mornings, but the bowels were not opened in the afternoon. The stools were pale yellow and liquid, and there was no blood or mucus. Liver injections were tried again, but with no relief. There was no loss of weight. She also suffered from frequency of micturition, pruritus vulvae, and cataract, all these symptoms being attributed to the diabetes. It was thought that the diarrhoea was due either to the diabetes or to a neoplasm of the colon.

Sigmoidoscopy did not show any abnormality. A barium enema (Dr. A. Jenkins) revealed a fistulous communication between the colon, in the region of the hepatic flexure, and the gall-bladder. The opaque material passed along what was thought to be the common duct, where there was a filling defect which was believed to be a stone at the ampulla of Vater (see illustration).

Operation was carried out November 16, 1951, and the findings were exactly as had been suggested radiologically. The hepatic flexure of the colon was adherent to the liver, and when the two organs were separated the gall-bladder was brought into view and was seen to communicate with the colon by a fistula. The fistula was divided and the opening in the transverse colon closed in layers. The junction of the cystic duct and the common bile duct was identified, and these ducts and the common hepatic duct were seen to be dilated. The pancreas felt normal. The common bile duct was explored and a stone was removed from the lower end. Another stone was found in the right hepatic duct. The ducts were washed out with saline, and, after the patency of the ampulla of Vater had been confirmed by means of a sound, the gall-bladder was removed and a drain placed over the common duct.

Radiograph showing the filling defect.

The patient made an uninterrupted recovery. The diarrhoea stopped immediately and has not recurred since.

R. H. FRANKLIN, M.B., F.R.C.S.,
Department of Surgery, Postgraduate Medical School of London, W.12.

Serum Sickness

Antitetanus serum is given widely as a prophylactic measure in out-patient departments of general hospitals and by general practitioners throughout the country, and mild symptoms due to serum sickness are noted from time to time. The following case is interesting because of the splenic enlargement, a factor which may cause confusion in diagnosis from glandular fever and septicaemia. Splenomegaly has been reported in America, but apparently not in this country.

CASE REPORT

The patient, a girl aged 7 years, injured her left thumb so that the nail and pulp were hanging by a medial skin-flap. She was admitted to hospital on October 26, 1951, for suture under general anaesthesia, and was given a prophylactic dose of 1,500 international units of antitetanus serum subcutaneously into the right arm, and "distaquaine" penicillin 250,000 international units six-hourly. The wound healed and she remained very well and was discharged on October 31. She returned to the out-patient department the next day, when the thumb was dressed, and appeared quite well. On November 2, when she reported for further dressings, it was noticed that her temperature was 99.6° F. (37.6° C.), and on examination tender enlarged, firm glands were found in both groins and popliteal fossae. The spleen was palpable two fingerbreadths below the left costal margin, but was not tender. There was no rash.

The patient was admitted to a medical ward, and on further examination four hours later was found to have palpable glands in both anterior cervical triangles and in the left axilla. There was an area of skin in the left hypochondrium 4 in. (10 cm.) in diameter, bright pink in hue, but not irritating. She had no temperature at this time. Her throat was normal, and she had no clinical jaundice. There was no apparent infection, and glandular fever was suspected. Blood examination showed: red cells, 4,530,000; haemoglobin, 78%; leucocytes, 7,000; polymorphonuclears, 83%; eosinophils 1%; lymphocytes, 13.5%; monocytes, 2.5%. A Paul–Bunnell agglutination test was negative, as were the Widal and Brucella agglutination tests. The next day, November 3, the pink erythematous area on the trunk had disappeared, but the skin over the gland in the right groin was discoloured. No local infection was apparent. A vaginal swab was taken, which revealed no cause for the adenitis, and a course of penicillin was begun by injection into the right buttock.

On November 5 the glands were no longer tender, but the whole of the right buttock was red, though on palpation there was no tenderness. A few rubelliform spots were noticed on the abdomen. The penicillin was discontinued, the diagnosis of serum sickness having been made. On November 6 the buttock was normal in colour, but a rash was present on both legs. This consisted of circular lesions with pale centres encircled by red rings varying in size from 5 to 30 mm. in diameter. The rash spread down her legs and faded lastly from her feet on November 8.

The following tests were made on November 8 and 9: Antitetanus serum was diluted to 1/100 and 0.02 ml. was injected intradermally into the right forearm. Twenty minutes later a wheal measuring 12 mm. in diameter and a flare measuring 24 by 30 mm. were noted. Antitetanus serum was diluted 1/10 and one drop was inserted into the left conjunctival sac: there was no reaction or irritation. (Claiborn in 1932 tested 465 patients with conjunctival and intradermal tests: 5.6% were positive to both tests; 21.3% were positive to the intradermal test only. All patients positive to the conjunctival tests were also positive to the intradermal test.) Crystalline penicillin was diluted 1/100 and 0.02 ml. was injected intradermally into the left arm. Twenty minutes later there was no reaction.

Strazza (1946) reported delayed sensitization to penicillin similar to serum sickness. On a scratch test the reaction to penicillin 15,000 units per ml. was negative. Gordon (1946) reported three cases and reviewed the literature on reactions to penicillin simulating serum sickness. There was no reference to enlargement of the spleen, but one case had glandular enlargement. Scratch tests were sometimes positive.

Diphenhydramine hydrochloride was begun on November 9, 20 mg. being given four-hourly. The glands in her neck, axilla, and popliteal fossae were no longer palpable on November 10. The glands in the groin had decreased in size and were not tender, and the spleen could just be felt on inspiration. On November 12 the spleen was no longer palpable.

Peterson and Bishop (1947) treated serum sickness with diphenhydramine hydrochloride, giving 50 mg. or more, up to 100 mg., six- to eight-hourly, depending on results. As relapse may follow withdrawal, they suggested carrying on for three days to a week, depending on the condition of the patient.

COMMENT

There was no history of asthma, urticaria, or hay-fever in the family, and this was apparently the first injection of horse serum the child had had. The first sign was a slight fever discovered seven days after the injection, though it is possible that the glands and spleen had enlarged before this time. The rash appeared on the tenth day, and varied in type over the next five days. The only complaint during these manifestations of serum sickness was tenderness in the groins.

I wish to thank Dr. H. R. E. Wallis for permission to publish this case and Dr. M. Marshall, house-surgeon, who transferred the child under my care.

MARY WHITFIELD, M.B., Ch.B.

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Reviews

SURGERY OF THE OESOPHAGUS

Surgery of the Oesophagus. By R. H. Franklin, M.B., B.S., F.R.C.S. (Pp. 219; 90 illustrations. £2 2s.) London: Edward Arnold. 1952.

Mr. Franklin's pioneer work on the surgery of the oesophagus, doubtless inspired by his association with Grey Turner, is well known, and his book is bound to attract attention. His own most important contribution is in the account of the treatment of atresia of the oesophagus, in which he tells us that his were the first recorded successes outside the United States; at the time of writing he had eleven successes following primary anastomosis. This is a noteworthy achievement and emphasizes that, owing to carelessness or ignorance in diagnosis, many infants are still being deprived of the chance of survival by not being referred to a surgeon. It is interesting to note that he now recommends the transpleural approach; the original procedure of resecting several ribs and working extrapleurally recalls the early years of this century.

The book provides a concise and clear account of the problems of oesophageal surgery and can be read without effort. It is liberally illustrated, although two of the four coloured plates are useless and their omission might have lessened the cost of the book. An index of the illustrations should have been included.

A chapter is devoted to oesophagoscopy, and the author emphasizes the dangers of the examination. Although he mentions the importance of the correct position of the head for safe instrumentation, he gives no instructions, and indeed Fig. 46 shows both the head and the neck in full extension, a position in which introduction of the oesophagoscope is almost impossible and certainly dangerous. This figure should be replaced by a set of illustrations showing the varying position of the head and neck at the different stages of the examination.

The book is chiefly suitable for postgraduate students and general surgeons needing to acquaint themselves with the advances of oesophageal surgery. One remarkable omission is any reference to or analysis of the figures (either the author's or others') of operability, mortality, and prognosis after operation for carcinoma of the oesophagus.

R. C. BROCK.

E.N.T. INTRODUCTION

Diseases of the Ear, Nose, and Throat. By J. Douglas McLaggan, C.V.O., M.B., Ch.B.,(Aberdeen), F.R.C.S., and Josephine Collier, B.M., Ch.B.(Oxon), F.R.C.S. Second edition. General Practice Series. (Pp. 438; 149 illustrations. £1 17s. 6d.) London: H. K. Lewis. 1952.

The authors are to be congratulated on this the second edition of this work. It is intended for students about to be introduced to the subject and for the recently qualified, and both classes will greatly benefit from reading it. The text is refreshingly clear, largely owing to the correct choice of words. In its 422 pages the authors cover the whole ground of diseases of the ear, nose, throat, oesophagus, and bronchi; nothing is omitted, but there must be no skipping by the reader else he will miss sentences which, though short, contain considered opinions based on wide experience. As teachers the authors know it is better to make dogmatic statements than to enter into verbose discussions which tend to confuse—for example, "The practice of enucleating tonsils to relieve quinsy is dangerous and unsurgical."

The anatomy throughout is brief but clearly emphasizes what is important to the parts under consideration. Indeed the whole book is full of common sense, as may be seen in the informative paragraphs where, writing of Ludwig's angina, the authors say, "the rarity of the disease contrasts forcibly with the prominence given to it in textbooks." They stress the importance of bacteriology in the differential diagnosis of tonsil ulcerations; they might have added routine blood examinations. Writing of operations, they emphasize general principles, giving details of technique only for the simpler operations, and these are clearly illustrated.

The chapter on laryngeal paralyses reduces the whole complicated story to easily understood simplicity; these words also apply to the account of simple and malignant intrinsic growths. Lastly, the chapters on the bronchi and oesophagus maintain the high standard set by the rest of the work and are admirably illustrated by diagrams and radiographs. This is a most readable book and should be in the hands of those tackling the specialty and desirous of becoming experts.

W. M. MOLLISON.

HEART AND CIRCULATION

Disorders of the Heart and Circulation. Edited by Robert L. Levy, M.D. (Pp. 944; 368 figures. £4 11s. 6d.) London: Baillière, Tindall and Cox. 1952.

Although the publishers describe this work as a new book, many of the chapters are revised versions of those published previously in *Nelson's Loose-Leaf Medicine*; with several new ones they have been assembled in the form of a separate monograph for the convenience of those specially interested in cardiovascular disorders.

In arranging the sequence of the 34 contributions by 41 authors, the editor confesses that he found it impossible to adhere closely to an aetiological classification, but was influenced by anatomical, physiological, diagnostic, and therapeutic considerations as well. Despite this explanation, it is difficult to discern any significant design in the order of presentation, and the expressed hope that undue overlapping has been avoided is certainly not fulfilled. Thus more than half the introductory chapter on cardiocirculatory physiology is devoted to heart failure, and yet we have another whole chapter on the same subject by a different author. Then, in a 48-page chapter on diseases of the pericardium, Pick's disease is discussed fully (and very well); yet the next chapter is on "Chronic Constrictive Pericarditis." Continuing, we have Abbott's original article on congenital heart disease (116 pages) followed by a modern version in 60 pages by Bing. Rheumatic heart disease (Bland) is on both active rheumatic carditis and established valve lesions, and then the chronic valve lesions are given a chapter to themselves. Perhaps the best example of duplication occurs later in the book, when a chapter on cardiac neurosis is followed by one on neurocirculatory asthenia (subject matter the same).

Owing to the increasing complexity of medicine and the vast territory that has been opened up in recent years, it is often said that the day of the textbook by a single author is over. Before it is discarded for good, however, its advantages should be carefully noted, so that they may be retained in the polygenetic literature of the future. These advantages include uniformity of style and treatment, continuity, balance, and proper building up of the work, section by section, without gaps and without redundances, into a recognizable, pleasing, and comprehensive whole—in short, graceful, economical, and sound architecture. In the polygenetic book the editor is alone responsible for this architecture; in this respect he assumes a highly important role and should be fully aware of it. When Robert Levy says —referring to the contributors—"obviously, it is their book," one must agree, and that is partly the trouble.

But that is not all there is at fault. A single author seems more alive to the fact that he will be judged by what he has written; a multitude of authors give the impression that they do not care quite so much. It is the old story of the fewer men the greater share of honour, and its corollary. And so, even if the book is accepted as an unrelated series of 34 essays on various cardiovascular subjects, it does not compare favourably, chapter by chapter, with several well-known treatises on heart disease written by single authors. Now this is serious, because the chief theoretical reason for encouraging multiple authorship

(apart from the time factor) is the belief that one individual cannot be expected to cover a variety of subjects as well as a group of experts, each allotted his own special field. This is where the contributors must recognize their own responsibilities and the editor exercise his right of frank criticism.

Finally, there is the index. This one occupies 2% of the 944 pages and must have been compiled by an able and industrious lay professional. But was it checked by a cardiovascular expert? Under angina pectoris, for instance, we have

in aortic insufficiency	383
in aortic stenosis	381
in coronary disease	450
in coronary heart disease ..	442

and no page reference to angina in anaemia, diabetes, hypertension, paroxysmal tachycardia, mitral stenosis, myxoedema, pulmonary hypertension, syphilitic aortitis, or thyrotoxicosis. Six surgical treatments for angina are given a page reference, but is there no medical treatment? QRS appears in three guises, as a complex, interval, and wave—and so on. I believe that a single author, responsible for everything in the book, would either compile the index personally or would check it carefully for gaps and redundancies as well as for accuracy: not that this index is bad, but neither is it good. Thomas Nelson and Sons have printed the book very nicely, and the figures are excellently reproduced.

PAUL WOOD.

THROMBOSIS

The Pathogenesis and Treatment of Thrombosis: With a Clinical and Laboratory Guide to Anticoagulant Therapy. By Irving S. Wright, M.D. Modern Medical Monographs (Pp. 78; 27 figures. $3.) New York: Grune and Stratton. 1952.

This monograph is based on the George E. Brown Memorial lecture, presented before the American Heart Association in 1951. The demand for copies of the lecture far outran the number of reprints available, so that Dr. Irving Wright wisely decided to incorporate the material in a small book. He discusses clearly and concisely the modern views on blood coagulation, reducing into an easily comprehensible form the knowledge of the complex factors known to take part. He also briefly reviews the influence of physicochemical phenomena and morphological changes in the blood and vessels which may play an important part in the initiation of thrombosis. The relationship of malignant disease, familial traits, cold haemagglutinins, and cryptoglobulinaemia to the onset of clotting are ably discussed.

About half the monograph is devoted to the methods now available to combat the onset and sequelae of thrombosis; all the main anticoagulants, as well as some which are little used over here, are mentioned and their characteristics compared. Finally, the most widely used laboratory methods for the study of blood clotting and the control of anticoagulant therapy are set out in the appendix.

This monograph should be of interest to all concerned with the care and treatment of patients with thrombosis. Though it does not present any new concepts, both its theoretical discussions and practical applications are of value to the clinician and laboratory doctor. Since it was originally designed to be presented as the spoken word, it is both clearly expressed and easy to read.

H. PAYLING WRIGHT.

INJURIES OF THE SPINAL CORD

Les Traumatismes de la Moelle Epinière. By Daniel Mahoudeau. (Pp. 196; 33 figures. 1,250 francs.) Paris: Masson et Cie. 1952.

This short monograph was written with the intention of summarizing the results of recent work on injuries to the spinal cord, chiefly by English-speaking workers, and largely determined by their experiences of spinal cord injuries in the second world war. It is built round a sound bibliography and forms an excellent introduction to the subject, being a well-ordered and clearly set-out exposition of physiological principles. No statistics interrupt the even development of the subject.

From the practical point of view the volume fails on two accounts. First, the strict limitation of the subject to cord injuries and bare mention of cauda equina injuries robs it of much usefulness, as the two lesions are so commonly encountered together and the differential diagnosis, if not of immediate practical importance, is of great prognostic value. Secondly, there are no case histories. The apology tendered for this, that they would overburden the volume, is scarcely sufficient to justify such an important omission, for on them one is chiefly dependent for correlating and reinforcing the theoretical considerations as well as for practical guidance.

The author only outlines orthopaedic aspects of treatment. He does not mention stabilization of the spine after reduction of a dislocation. His account of nursing is rather general. Tidal drainage, though becoming less popular in Britain, receives pride of place in treatment of the paralysed bladder.

In short, this is an excellent study in applied physiology and an ideal book for a senior student particularly interested in neurology or a postgraduate beginning some special training in spinal injury. But it will only refresh the mind of the experienced neurologist.

J. G. BONNIN.

CHIROPODY

Chiropodial Orthopaedics. By Franklin Charlesworth, F.Ch.S. Foreword by Sir Harry Platt, M.S., F.R.C.S., F.A.C.S. (Pp. 255; 131 figures. £1 5s.) Edinburgh: E. and S. Livingstone. 1951.

The author of this well-written book has qualifications which must be almost unique, for in addition to a practical knowledge of surgical boot-making and years of experience as the head of an active school of chiropody (one of a number which have failed to survive the advent of the Welfare State), he has handled many hospital patients with really troublesome feet. Mr. Charlesworth describes his techniques in the concise manner of a good teacher, and the text is freely illustrated. Most of the chapters are on matters of interest not only to chiropodists and orthopaedic surgeons but also to surgical technicians and boot-makers. But many of the problems and the methods of dealing with them are well outside the field of chiropody: lobster feet requiring special insoles and surgical shoes is a typical example.

Considering he is a qualified chiropodist, the author expresses a fine scorn for felt pads and strapping in prolonged contact with the foot. Some of the removable appliances he describes are similar to those obtainable under N.H.S. schedules, but others require so much personal skill and care that they are not likely ever to be freely obtainable. This applies particularly to Mr. Charlesworth's moccasin technique for the protection of tender areas and for filling up the space of missing toes; a soft leather moccasin is made to cover the foot and is then built up in certain places, often by applications of milk rubber latex, to a form which can be accommodated in a shoe of acceptable shape. Strangely enough, the author does not mention that useful addition to a sturdy walking shoe, a steel plate inserted lengthwise between the layers of the sole in order to prevent any buckling at the tread in cases of hallux rigidus, march fracture, osteochondritis of a metatarsal head, or amputation of the great toe.

As consultant chiropodist to the Hope Hospital, Salford, the author naturally favours a department of chiropody in every large general hospital, and in the final chapter he describes his own clinic, which appears to thrive in happy symbiosis with the orthopaedic department. But Mr. Charlesworth has come up the long and hard way, and the chances are slender that other men will follow his lead and acquire such a combination of special skills.

K. I. NISSEN.

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SILICA OR COAL?

All miners, no matter what mineral they are occupied in extracting, are exposed to some dust derived from rock, and almost all such dusts contain silica, partly free and partly combined in the form of silicates. Since free silica causes fibrosis in experimental animals, while other mineral dusts are either much less fibrogenic or entirely non-fibrogenic, it is natural that pulmonary fibrosis in miners should be attributed to the free silica in the dust. The classical type of silicosis with whorled collagenous nodules, giving rise to the characteristic nodular picture in radiographs of the chest, is found only in men exposed to dusts containing a high proportion of free silica, as in the gold mines on the Witwatersrand. It was chiefly the increasing use of radiography that led to the recognition that pulmonary fibrosis also occurred in workmen exposed to various dusts with a relatively low free silica content. But the appearance of these "mixed-dust pneumoconioses" both pathologically and radiologically was different from that of silicosis, and the question arose whether the fibrosis was due to silica modified in its effect by admixture with other components of the dust or whether these other components were themselves contributing to, or even responsible for, the fibrosis.

This question has been most keenly debated and thoroughly investigated in relation to the pulmonary fibrosis found in coal-workers. In this country the non-committal term "coal-workers' pneumoconiosis" has been applied to this disease in order to leave its pathogenesis open, but in America and on the continent of Europe the terms "anthraco-silicosis," "silico-anthracosis," or plain "silicosis" are used with the implication that the disease is fundamentally a form of silicosis. These opposing points of view were debated at a conference on silicosis held at the Silicosis Research Institute at Bochum,[1] and some of the evidence put forward by both sides is discussed below.

Pathological studies of the lungs of coal-workers[2-4] have shown that there is a progressive series of histological lesions ranging from the typical whorled silicotic nodule of the rock-worker to deposits of coal dust in foci throughout the lung, and in the peribronchial and subpleural lymphatics, with little or no collagenous fibrosis and only a slight reticulin reaction. While silica may be responsible for the collagenous fibrosis in the intermediate type of nodule, Heppleston[5] has recently argued that the coal "macule," without collagenous fibrosis, develops in response not to the minute quartz content of the coal but to the coal substance itself, and that the later development of collagen in these deposits is simply due to the advancing age of the lesion. Supporters of the siliceous origin of mixed dust pneumoconioses[6 7] maintain that free silica, even in very small amounts, is always responsible for any significant fibrosis and that these non-fibrous, impalpable deposits of coal dust should not be regarded as falling within the realm of pathology. It was Arnold[8] who, in 1885, first distinguished "anthracosis simplex" from "anthracosis indurativa." Rüttner[7] dismisses the soft nodules of anthracosis simplex as "a mere soiling (*blosse Verschmutzung*) of the lung" and, like Gardner,[9] maintains that they have no effect upon the function of the lung. However, simple nodular silicosis has also been found to have no significant effect upon lung function,[10 11] yet no one would deny that it was a pathological condition. Gough[3] and Heppleston[12] have emphasized that in the course of time focal emphysema may develop in and around the coal macules, and that this must result in some disturbance of function. Severe disability in coal pneumoconiosis is largely confined to men with massive fibrosis,[10 13] which develops only in those who already have simple pneumoconiosis. A "mere soiling" of the lung which may have such serious aftermaths is surely a pathological condition.

The advocates of the siliceous origin of coal pneumoconiosis take their strongest stand on the fact that animal experiments—whether carried out by intratracheal, subcutaneous, or intraperitoneal injection or by inhalation—have with few exceptions[14 15] shown that pure coal dust produces no fibrogenic reaction, but here the argument appears self-contradictory. Collis and Gilchrist[16] and Gough[17] first showed that coal-trimmers who are exposed to such pure coal dusts do in fact develop pulmonary fibrosis, and Wright[18] has shown that after the inhalation of large quantities of coal dust, collected at a coal face where the prevalence of pneumoconiosis is high, rats do not develop even a reticulin reaction in the lung approaching that found in the coal focus in man.

Negative animal experiments cannot disprove the fibrogenic action of a dust in man. It is possible that the experiments have not extended over a long enough period or, more likely, that the reactions of

human and animal lungs differ. It may be argued that since silica does produce fibrosis in the lungs of animals it should do so even in the presence of coal if it is the silica that is responsible for the fibrosis in man. Alternatively, the human lung must be more susceptible to minute amounts of silica in association with coal than is the animal lung. If this were so the administration to animals of coal enriched in silica (by the admixture of a small amount of quartz) should produce lesions resembling the coal focus in man. Such experiments have recently been reported by King and his colleagues.[19] Using intratracheal injection, they found that 2 mg. of quartz caused no fibrosis in the lungs of rats, since it was removed to the hilar lymph nodes, where some fibrotic nodules appeared. One hundred milligrams of pure anthracite or graphite dust remained in the lung, producing no significant fibrosis. But when 2 mg. of quartz was mixed with 98 mg. of coal nodular foci of reticulinosis developed. The authors suggested that the large amount of coal upset the lymphatic drainage so that the silica was retained in the lung to produce its toxic effect. While this conclusion is justified their experiments throw no light on the relative roles of coal and silica in human pneumoconiosis. They only suggest, not unreasonably, that a man exposed to a negligible hazard from pure silica might be worse off if he also had to inhale much coal dust, or that a coal-miner who also does some rock work may get more pulmonary fibrosis than a worker on a pure coal face. Moreover, dusts administered by intratracheal injection may behave differently from inhaled dusts. Mavrogordato,[20] using the inhalation method, found that a mixture of coal dust and silica caused less fibrosis in the guinea-pig's lung than the same amount of silica alone.

What is needed now is information on the pathological changes occurring in men exposed to high concentrations of pure carbon dust. Such exposure occurs in the manufacture of carbon black and of carbon-arc electrodes. Fifteen years ago Locktemper[21] and Hollman[22] showed that workers in the carbon-black industry develop radiological abnormalities similar to silicosis. Recently Brauss and Gärtner[23] have confirmed these observations, finding radiological changes in soot-workers identical with those in coal-workers' pneumoconiosis, including both simple nodulation and massive shadows. Koelsch[1] reported similar findings in workers making carbon electrodes. Unfortunately, and mysteriously, none of these cases has yet been investigated pathologically. Until this has been done there is no certainty that pure carbon can produce pulmonary fibrosis in man. But the close association shown by Gough[24] between radiological and pathological findings in coal-miners suggests that when at last a pathological account of soot-workers' lung is published it will tell a story of changes closely resembling those found in coal-workers. The present assumption that carbon is a wholly innocuous dust on inhalation may then finally be shown to be wrong.

This debate is not only of theoretical interest, for it has important practical consequences. In this country, recognition that coal dust itself may cause disabling pneumoconiosis has led to a vigorous campaign of dust suppression at the coal faces of all mines where dust concentrations, regardless of their silica content, rise above an approved level of 650 particles per c.cm. in anthracite and 850 in other coal mines. In the U.S.A., too, measures are taken to suppress all dust in mines, but the suggested levels of safety are still related to the silica content. Rüttner[7] advocates judging the hazard of any dust upon a mineralogical and chemical measurement of the silica content. This insistence on the orthodox silica theory was also shown by nearly all the German experts in the discussion[1] at Bochum to which we have referred, and it affects their mining practice. In German coal mines dust suppression is concentrated on rock dust, and coal dust is regarded as being harmless. This attitude is carried to remarkable lengths. Worth and Dickmans,[25] in a survey of 350 miners, found as much radiological abnormality in relation to years worked underground in men who had only worked on the coal face as in men who had also worked in rock. They conclude that rock dust must be carried on to the coal face from other parts of the mine to produce disease in the men working there. Koelsch alone among the German experts sounded a note of warning based on his experience among workers exposed to pure carbon dust, and agreed with the view that coal dust itself might be

1 *Bericht über die Medizinische-wissenschaftliche Arbeitstagung über Silikose, Bochum*, 1951. *Beitr. z. Silikose-Forschung*, 1951.
2 Belt, T. H., and Ferris, A. A., *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, 1942, No. 243, p. 203.
3 Gough, J., *Occup. Med.*, 1947, **4**, 86.
4 di Biasi, W., *Bericht über die Medizinische-wissenschaftliche Arbeitstagung über Silikose, Bochum*, 1951, p. 151.
5 *Arch. industr. Hyg.*, 1951, **4**, 270.
6 Watjen, J., *Arch. Gewerbepath. Gewerbehyg.*, 1933, **4**, 310.
7 Rüttner, J. R., *Vjschr. naturf. Ges. Zurich*, 1950, **95**, Beiheft 2/3, 73.
8 *Untersuchungen über Staubinhalation und Staubmetastase*, Vogel, Leipzig, 1885.
9 *3rd Saranac Symposium*, 1937.
10 Wright, G. W., *Occup. Med.*, 1946, **2**, 546.
11 Rossier, P. H., Bucher, H., and Wiesinger, K., *Vjschr. naturf. Ges. Zürich*, 1947, **92**, Beiheft 3/4, 83.
12 *J. Path. Bact.*, 1947, **59**, 453.
13 Cochrane, A. L., Fletcher, C. M., Gilson, J. C., and Hugh-Jones, P., *Brit. J. industr. Med.*, 1951, **8**, 53.
14 Argyll Campbell, J., *Brit. J. exp. Path.*, 1944, **25**, 46.
15 Ravvin, V. A., and Enyakova, P. A., *Arkh. Patol.*, 1951, **13**, 79.
16 *J. industr. Hyg.*, 1928, **10**, 101.
17 *J. Path. Bact.*, 1940, **51**, 277.
18 *Bericht über die Medizinische-wissenschaftliche Arbeitstagung über Silikose, Bochum*, 1951, p. 119 (quoted by C. M. Fletcher).
19 *Brit. J. industr. Med.*, 1951, **8**, 62.
20 *S. Afr. Inst. Med. Res.*, Publ. No. 15, 1922.
21 *Verh. dtsch. Ges. inn. Med.*, 1936, **48**, 154.
22 *Röntgenpraxis*, 1937, **9**, 32.
23 *Med. Welt*, 1951, **20**, 253.
24 *J. Fac. Radiol. (Lond.)*, 1949, **1**, 28.
25 *Tuberkulosearzt*, 1950, **4**, 495.

fibrogenic. "We have not got so far in scientific investigation in Germany," he said, "that the problem can yet be considered to be finally settled." Until it is settled the British term "coal-workers' pneumoconiosis," which leaves the question of pathogenesis open and concentrates attention on the coal dust which has been shown to cause the disease, is greatly to be preferred to anthraco-silicosis or, worse still, plain silicosis.

SEROUS HEPATOSIS

Two varieties of hepatic cirrhosis have hitherto been recognized as associated with, or resulting from, malnutrition: the diffuse fibrosis that follows prolonged severe fatty infiltration, and the less regular form with nodular hyperplasia that follows non-fatal massive hepatic necrosis. Both are readily produced in experimental animals, the former by diets deficient in lipotropic factors, and the latter by diets deficient in the thio-amino acids and vitamin E. In our opening pages this week Professor K. R. Hill and his colleagues draw attention to a third variety, in which neither fatty infiltration nor liver-cell necrosis appears to play any significant part in pathogenesis. Their discussion springs from the study of 150 cases of liver disease in Jamaican children. The disease apparently passes through three phases, acute, subacute, and chronic, and about one-third of their cases fell in each category. The phase at which the children were first seen correlated roughly with the patient's age, the acute cases occurring in the youngest and the chronic cases in the oldest; most were aged between 1 and 3 years. In the acute stage the child is obviously ill, with a large tender liver and ascites as the outstanding features. In the subacute phase the children do not appear ill, but the liver is enlarged, although ascites is often absent. In the chronic stage the clinical picture is that of hepatic cirrhosis with the usual complications due to portal hypertension.

The anatomical evolution of the hepatic lesion has been followed in many cases by serial biopsies, and the sequence of events is clearly depicted. In the early stages there is a conspicuous distension of the perisinusoidal spaces of Disse, which appear histologically to be filled with a protein-rich fluid. At a later stage a strongly eosinophil coagulum occurs within Disse's space in many places, and in association with this coagulum reticulin fibres appear in excess of those normally present in this situation. An extension of this sequence of changes to the spaces of Mall in the portal tracts and around the inter- and intralobular vessels gradually results in an extensive diffuse fibrosis. This is further enhanced by fibroblastic invasion of the coagula, the resultant fibrosis producing the distortion and destruction of the normal lobular architecture characteristic of cirrhosis. It is apparently only in these more advanced stages that the parenchymal cells show evidence of severe degeneration or necrosis. Fatty change, with few exceptions, is insignificant throughout the course of the disease.

This sequence of events is strongly reminiscent of the condition termed serous hepatitis by Roessle[1] and Eppinger,[2] in which the perisinusoidal spaces become conspicuous owing to their distension by a protein-rich fluid. Although these authors did not actually observe the evolution of this condition into cirrhosis, they both emphasized the impairment of nutrition of the liver cells that must result from interposition of a further barrier between the cells and their blood supply as well as the interference with the adequate removal of metabolites. Keschner and Klemperer,[3] however, strongly criticized the concept that serous hepatitis is an important precursor of fibrosis, since they found a similar condition in 15% of a large series of necropsies. As they found, moreover, that 36% of their cases of heart failure showed the same picture, they were inclined to dismiss both the term serous hepatitis, with its implication of an underlying inflammatory aetiology, and the condition itself as an important precursor of fibrosis. The frequency with which a similar state seems to occur agonally, to which Popper[4] has drawn attention, would seem to support this attitude. The development of hepatic cirrhosis in cases of long-standing congestive cardiac failure—so-called cardiac cirrhosis—in which the histological picture of serous hepatitis is so frequently seen, draws attention to the importance of the time factor in liver pathology. If a hepatic lesion is of short duration, recovery from it is often complete and without scarring. The same lesion, or even one of lesser extent, if present beyond a certain minimum length of time, leads to irreversible change accompanied by fibrosis. This is well seen in cases of carbon tetrachloride injury, fatty infiltration, and congestive heart failure, and undoubtedly is of great importance in the Jamaican children.

Two points of especial interest in this work from Jamaica—and there may be a connexion between them—are the remarkable rarity of fatty infiltration (only 5 of Hill's 150 cases) and the cause of the

[1] Roessle, R., "Entzündungen der Leber" in F. Henke and O. Lubarsch's *Handbuch der Speziallen Pathologischen Anatomie und Histologie*, **5**, 243. Berlin: Springer. 1930.
[2] Eppinger, H., *et al.*, *Die Seroese Entzündung; eine Permeabilitäts Pathologie*. Vienna: Springer. 1935.
[3] *Arch. Path. (Chicago)*, 1936, **22**, 583.
[4] Ibid., 1948, **46**, 132.
[5] Evans, W. C., and Evans, E. T. R., *Nature, Lond.*, 1949, **164**, 30.
[6] Popper, H., *Z. klin. Med.*, 1937, **131**, 161.
[7] Eppinger, H., and Leuchtenberger, R., *Z. ges. exp. Med.*, 1932, **85**, 581.

accumulation of protein-rich fluid in the spaces of Disse. The diet of the affected children was both tragically monotonous and deficient in protein—animal and vegetable. In all other parts of the world where similar diets are taken, the outstanding hepatic lesion, at least in the early stages, is fatty infiltration. Despite many detailed studies, serous hepatitis has not been observed in these other areas. Yet in Jamaica an essentially similar diet produces not fatty infiltration but serous hepatitis. An important dietary difference may lie in the various vegetable infusions or "teas" which appear to be consumed in large quantity by these Jamaican children, and the toxicity of these infusions is now being investigated. The hepatic necrosis caused by ingestion of the alkaloids of *Senecio* (ragworts)[5] points to the possible importance of such a line of inquiry. The enhanced susceptibility to many liver poisons that results from dietary protein deficiency may well be a factor in restricting the condition to people whose nutrition is inadequate. Even if this is the true explanation of the facts, the anatomical effect of the toxic agent is distinctly unusual. The great majority of hepatoxic substances cause necrosis of liver cells as the most conspicuous lesion. In the "serous hepatosis" in Jamaica the absence of parenchymal necrosis is conspicuous, and the outstanding lesion appears to be an increase in permeability of the sinusoidal endothelium. But, since a similar histological appearance can be produced experimentally with allyl formate[6] or histamine,[7] the postulated properties of the hypothetical poison are by no means unique.

ASPIRATION PNEUMONIA AND BRONCHIECTASIS

The many current theories about the aetiology of bronchiectasis reflect the uncertainty about the exact mode of production of this disease. Bronchial dilatation can be caused, it has been postulated, by developmental abnormalities, by destruction and weakening of the bronchial walls by infection, by traction from peribronchial fibrosis, or by mechanical factors following pulmonary collapse. As we have previously commented, the view that bronchiectasis is commonly congenital in origin is now less widely held.[1] Although it cannot be denied that bronchiectasis sometimes arises from an abnormal development of the bronchial tree, such cases are exceptional, and even many of the cases of so-called "congenital cystic disease of the lung" are probably acquired after birth.[2] The relative importance of the other factors in causing bronchiectasis remains uncertain. Confusion has probably arisen from the problem being approached in different ways. The clinician, with an eye to the progress of the patient and the radiographic changes in the bronchial tree, has focused his attention on the calibre of the bronchi and been drawn to the mechanical theory of bronchial dilatation, sometimes without due regard to the pathological changes in the lung. The pathologist, on the other hand, from histological studies, has emphasized the inflammatory and fibrotic appearance of the bronchial walls and surrounding lung, and has tended to regard such changes as being primarily responsible for initiating bronchial dilatation. Again, as Whitwell[3] has recently suggested, the diversity of these views might indicate that bronchiectasis is not a single disease but only a common feature of a number of distinct pathological processes. From a study of 200 lung specimens removed at operation Whitwell found it possible to separate three pathological varieties of bronchiectasis, and correlation with the clinical findings in these patients suggested that the varieties were aetiologically distinct. He gave the name "follicular" to a type of bronchiectasis which, occurring in young patients, often followed measles or whooping-cough; in these cases subepithelial lymph-follicle formation and peribronchial interstitial pneumonia dominated the histological picture. It was thought that the disease began as a diffuse bronchiolitis following acute viral infections in childhood. In the second variety, bronchiectatic saccules were formed by the bulbous ends of the branches of the segmental bronchi, the intervening lung parenchyma remaining normal and fully aerated. This type of "saccular" bronchiectasis was found in older patients, and it was thought to start as a mural inflammation of the medium-sized bronchi, with consequent destruction of the bronchial walls. The initial infection was not severe enough to affect the alveoli, so collateral ventilation remained normal, and there was no alveolar collapse. The third variety, "atelectatic" bronchiectasis, included those cases where lobar or segmental bronchial dilatation was associated with pulmonary collapse. Stimulating as these findings are to the study of bronchiectasis, it must be noted that Whitwell was able to fit only about half of the specimens examined into one of these three categories, and it is not altogether surprising that some specimens showed features common to both follicular and atelectatic bronchiectasis.

Most clinicians agree that there is a close association between pulmonary collapse and bronchiectasis,

1 *British Medical Journal*, 1949, 2, 970.
2 Oswald, N., and Parkinson, T., *Quart. J. Med.*, 1949, 18, 1.
3 *Thorax*, 1952, 7, 213.
4 Scadding, J. G., *Lancet*, 1948, 1, 89.
5 *British Medical Journal*, 1951, 2, 1018.
6 Crofton, J. W., *et al.*, Ibid., 1951, 2, 1368.
7 Ibid., 1953, 1, 68.

and there is ample evidence that the atelectasis occurring in such diseases as whooping-cough and primary tuberculosis often gives rise to bronchiectasis. Elsewhere in this issue of the *Journal* Drs. K. D. F. Morle and Squadron Leader P. W. Robertson describe investigations which show that bronchiectasis may also follow simple aspiration pneumonia. By doing serial bronchograms on 300 patients with this disorder they were able to demonstrate the development of bronchial abnormalities in over 60% of the patients. In most instances the bronchi returned to normal, but in 5% an established bronchial abnormality persisted for more than 18 months after the original pneumonia. It is fair to assume that most of these patients had developed permanent bronchiectasis as a result of their pneumonia, although it is possible that there had been a previous bronchial abnormality in some patients. This finding emphasizes once again the importance of understanding simple aspiration pneumonia.

Aspiration pneumonia may be defined as collapse and inflammation of a broncho-pulmonary segment following mechanical obstruction to a bronchus by the retention or aspiration of infected secretions.[4 5] It is a common complication of catarrhal disorders of the respiratory tract; it is usually a benign illness which responds rapidly to postural drainage and chemotherapy. This type of pneumonia has been slow to achieve general recognition because it is often confused with virus pneumonia and because it can be diagnosed with certainty only by accurate radiographic location of the pulmonary lesion. Yet benign aspiration pneumonia is probably the commonest type of pneumonia encountered in present-day hospital practice.[6] Last week Dr. John Fry reviewed in this *Journal*[7] a series of patients with acute lung disease which he had seen in general practice. During a period of two years he found only seven cases of lobar pneumonia as compared with 70 who had a mild pneumonic illness. Of these, no fewer than 21 patients had an illness which conformed to the accepted pattern of aspiration pneumonia. It is evident that aspiration pneumonia is not only a common condition but also one which can give rise to bronchiectasis as a late complication.

SUCCINYLCHOLINE

The chemist and pharmacologist are continually presenting the anaesthetist with new tools to help him to solve the problem of how to obtain safe and selective muscular relaxation without the need to depress cerebral function by deep narcosis or endanger life by prolonged depression of the respiratory muscles. A compound recently used for these purposes is succinylcholine; chemically it resembles two molecules of acetylcholine lying alongside one another. It is valuable because it produces a muscular relaxation that is profound but normally of a very short duration, and allows manœuvres such as intubation to be safely carried out. Unfortunately in a few patients the action of succinylcholine is not so short-lived, and prolonged cessation of respiration (apnoea) may result. A possible explanation of this abnormal reaction is discussed in two papers in this issue by Dr. H. Lehmann and his colleagues. The findings confirm earlier observations[1 2] that the prolonged action of succinylcholine is seen in patients who have an unusually low level of serum pseudo-cholinesterase. The evidence now presented suggests that injection of a preparation of concentrated human serum which is sufficient to increase significantly the pseudo-cholinesterase activity of the blood will at the same time reduce this period of apnoea in these sensitive patients. It is unfortunate that it was not demonstrated that successive injections of succinylcholine would produce similar periods of apnoea in the absence of injected enzyme, so that there would then remain no doubt that the shorter period of apnoea after the second dose and following the plasma infusion was directly related to the rise in pseudo-cholinesterase activity so produced. Similar attempts[3 4] have been made in animals to raise the level of the true cholinesterase by adding concentrated enzyme preparations, but these have shown little or no effect on the rate of destruction of acetylcholine. It is therefore unlikely that such infusions would be of any value in the treatment of poisoning by anticholinesterase substances such as some of the modern insecticides or war gases. It seems probable that succinylcholine exerts its effects by occupying the sites on voluntary muscle normally occupied by the acetylcholine produced in response to a nerve impulse which contracts the muscle. But the mechanism for destroying succinylcholine is less efficient, so that a longer-lasting block occurs, and further impulses cannot affect the muscle until the succinylcholine has disappeared to leave room for acetylcholine. Acetylcholine is destroyed by both true cholinesterase and pseudo-cholinesterase, but succinylcholine only by the latter.

The means whereby the succinylcholine is removed from the muscle remain uncertain, except that there is diffusion back into the blood, because we do not know whether pseudo-cholinesterase exists in the muscle or at the myoneural junctions in man. In view of the interest in cholinesterase and substances that interfere with its action it is surprising how little information there is on the amounts of these enzymes present in the different tissues. Only Thompson and his colleagues[5 6] seem to have attempted a survey, and this includes rat tissues and only the central nervous system of man. As true cholinesterase cannot reach the myoneural junction from outside it is unlikely that pseudo-cholinesterase

1 Bourne, J. G., *et al.*, *Lancet*, 1952, **1**, 1225.
2 Evans, F. T., *et al.*, ibid., 1952, **1**, 1229.
3 Beck, I. T., *Brit. J. Pharmacol.*, 1951, **6**, 144.
4 —— ibid., 1952, **7**, 482.
5 Ord, M. G., and Thompson, R. H. S., *Biochem. J.*, 1950, **46**, 346.
6 —— —— ibid., 1952, **51**, 245.
7 *Nature, Lond.*, 1952, **170**, 617.

added to the blood will be any more successful. The effect of raising the amount of enzyme in the blood is probably to increase the speed at which the blood level of the drug falls so that no more can reach the muscles. It would therefore be interesting to know if human muscles do in fact contain pseudo-cholinesterase and, if so, whether the level here varies as it does in the serum. The attempt made to compare the action of succinylcholine in man and dogs on the basis of the cholinesterase activities of their bloods will not bear critical examination. Before jumping to any conclusions about these observed differences in man and dog in their response to succinylcholine it would be as well to bear in mind the comment recently made by Zaimis[7]: "Hitherto it has generally been assumed that results obtained from experiments on one mammal could safely be regarded as typical for mammals in general. It is now clear that results obtained from the muscles of any one mammalian species are valid only for this species and perhaps for the particular muscle upon which the experiments were made." Dr. Zaimis was discussing the results of her observations on the action of decamethonium and succinylcholine on muscles.

THE TREATMENT OF VENTRICULAR FIBRILLATION

Increasing interest has recently been shown in the treatment of cardiac arrest during operation, a subject always of importance to surgeons and anaesthetists since the dangers of chloroform were first recognized, and now of particular significance while operations are being performed on the heart itself. Such operations and those on the adjacent thoracic viscera have given opportunities for direct observation of the heart and have allowed the differentiation of two catastrophes—cardiac arrest and ventricular fibrillation. In cardiac arrest, or ventricular asystole, there is complete cessation of all heart action. In ventricular fibrillation the ventricular muscle contracts in an irregular and uncoordinated fashion, producing rippling movements which can be easily seen or felt but which are ineffective, causing no beat and no pulse. The two conditions thus cannot be distinguished except by direct observation of the heart or by electrocardiography, and so when the heart stops during an abdominal or limb operation it is impossible to tell in which fashion it has done so. The effect of ventricular fibrillation is as serious as that of asystole, since it is never spontaneously reversible.

The established treatment for cardiac arrest is cardiac massage. An essential adjuvant is the maintenance of adequate oxygenation by artificial respiration with pure oxygen. Cardiac massage has two possible effects: first, it stimulates the heart mechanically; secondly, it provides a limited circulation. The heart itself and the brain cannot survive undamaged if their blood supply is cut off for more than a very few minutes—probably four minutes is the maximum[1]—whereas other organs are much more tolerant, the liver and kidney surviving up to about thirty minutes' ischaemia. Compression of the aorta below the origin of the carotids concentrates the blood flow to the coronary vessels and the brain and so should be done if feasible. The heart cannot be massaged efficiently through the intact pericardium. If the chest is open, it is a simple matter to incise the pericardium; if not, the approach is through the upper abdomen, dividing the diaphragm and pericardium through the adherent area, or perhaps preferably by a left-sided intercostal incision through the fourth space, with division of costal cartilages. Massage should always be started as soon as possible after arrest has been diagnosed.[2] The injection of various drugs into the cavity of the heart is usually recommended, sometimes before massage is started, but the importance of maintaining a circulation is so great that massage must not be delayed. Pride of place is usually given to adrenaline. This is probably a mistake, for it has recently been shown[3,4] that the action of adrenaline on the anoxic heart muscle is to cause ventricular fibrillation; it should therefore be avoided. Calcium chloride, 10%, increases the irritability of the heart, and is perhaps of value,[5] but there is no known drug proved to remedy this condition. Once the heart's action is restored, it is important to maintain an adequate systemic blood pressure. For this purpose continuous administration of vasoconstrictor drugs such as methedrine or *nor*adrenaline may be necessary for several hours.

The same measures have been recommended in the past for the treatment of ventricular fibrillation. It has long been known that ventricular fibrillation can be stopped in the experimental animal by an electric shock. A powerful electric current of short duration passed through the ventricles causes a complete tetanic contraction, which is usually followed by resumption of normal beat. There have been several reports from America of this procedure applied to human patients,[6] and recently McMillan, Cockett, and Styles[3] at St. Thomas's Hospital have published the first account from Britain. They describe a simple apparatus, working off the mains, capable of giving a series of interrupted shocks of various voltages, which was found to succeed in dogs without causing serious damage to the heart. Its use in three human patients is reported; in each case the fibrillation was abolished. In the first two after about half an hour asystole occurred and the patients died. In the third normal rhythm was restored and persisted, and this patient recovered; his recovery was not complete, for he showed evidence of cerebral damage, and an electrocardiogram suggested an anterior myocardial infarct. The electric apparatus is an ancillary method of treatment; cardiac massage should be used before it is tried and if necessary after, and full oxygenation maintained throughout. Beck, whose experience is very wide, has stated, "The beat can be restored in every normal heart."[7] By speedy diagnosis and rapid action many of these surgical tragedies can be avoided.

[1] Dale, W. A., *Ann. Surg.*, 1952, **135**, 376.
[2] Bost, T. C., *Amer. J. Surg.*, 1952, **83**, 135.
[3] McMillan, I. K. R., *et al.*, *Thorax*, 1952, **7**, 205.
[4] Barber, R. F., and Madden, J. L., *Amer. J. Surg.*, 1944, **64**, 151.
[5] Kay, J. H., and Blalock, A., *Surg. Gynec. Obstet.*, 1951, **93**, 97.
[6] Beck, C. S., and Rand, H. J., *J. Amer. med. Ass.*, 1941, **141**, 1230.
[7] *Veterans Adm. techn. Bull.*, 1950, TB 10–65.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

THE PREVENTION AND TREATMENT OF TETANUS

BY

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Tetanus or lockjaw is one of those comparatively rare diseases which are liable to crop up unexpectedly in practice. In England and Wales the Registrar-General's Review shows that for the decade 1940–9 an average of 84 fatal cases occurred per annum, which probably represents a total case incidence of between 160 and 200 per annum. For comparison in 1949 there were 79 deaths from tetanus and 84 from diphtheria. Since prevention among civilians depends on giving antitoxin as soon as possible after wounding, and the successful outcome of treatment may depend on early diagnosis, it is clear that a considerable burden of responsibility falls on general practitioners. What happens subsequently after the patient has been admitted to hospital, though more dramatic, has less effect in deciding the issue of prevention or cure.

In considering this subject the logical sequence would be to study first the causal organism, the type of individual at risk, and the kind of wound likely to cause the disease: next to describe methods of prevention; and finally the symptomatology, diagnosis, treatment, and prognosis of the disease. This sequence will be followed here, with particular emphasis on prevention and diagnosis.

Clostridium tetani, the causal organism of tetanus, produces spores which are highly resistant and may remain dormant for years outside the body and for months in the tissues when conditions for development are unsuitable. They are commonly present in cultivated soil and also in the intestinal tract and excreta of man, the horse, and other animals. Manure and horse ploughing may help to disseminate infection, and the degree of infectivity of the soil is one of the factors which determines the incidence of the disease. Germination of spores only takes place under anaerobic conditions. In wounds it is helped by tissue trauma, necrosis, foreign bodies, and pyogenic or other anaerobic infection, but the determining factor is a sufficiently low oxygen tension. When growth occurs an exotoxin is produced which is absorbed by the blood stream and reaches the nervous system producing the characteristic symptoms. The evidence suggests that once the toxin has become "fixed" to the motor cells it cannot be neutralized by antitoxin. Circulating antitoxin can only prevent further absorption of toxin from the wound and neutralize toxin which has not already reached the motor cells.

Type of Wound and Type of Patient

In civilian practice in this country tetanus hardly ever follows serious wounds because prophylactic antitoxin is almost always given to such and affords protection. Instead it is caused by relatively slight injuries in patients who for one reason or another have not been given antitoxin. Thus it commonly follows septic infections such as whitlows, dirty abrasions, or slight penetrating wounds as from a thorn, splinter, garden fork, or nail in boot. Such injuries have usually become infected and sealed by scabs forming a cavity where anaerobes can grow, and injuries such as these account for about 80% of all cases. Occasionally clean cuts sustained in a field or garden are a cause. The remainder arise from a miscellaneous collection of lesions such as umbilical sepsis causing tetanus neonatorum, puerperal sepsis, infection in body cavities such as the middle ear or maxillary antrum, and septic skin lesions such as impetigo, dermatitis of the scalp, or varicose ulcers. Abscesses or ulcers in the intestinal tract may be the source and probably account for some of the so-called idiopathic cases. Sometimes the wound is so slight that it has healed before the disease develops. Finally there is a small group, now happily becoming smaller, in which tetanus is due to infected materials used in medicine or surgery. These have included surgical instruments, catgut, wool or felt, material for intramuscular injections, vaccination lymph, or even sulphonamide dusting-powder infected by the cardboard containers in which it was packed.

Tetanus may occur at any age, and men are affected three times more commonly than women chiefly because of their greater liability to infected wounds. The majority live and work in agricultural districts in occupations such as farm labourers, grooms, farmers, gardeners, which involve manual contact with soil or manure. Children develop it as a result of abrasions or cuts which have not been kept clean, and old people from uncleanliness combined with slight wounds of the hands and feet.

Passive Immunization

Two methods of prevention are now known: by passive and by active immunization. In civilian practice the former is the only method in general use, and this will be considered first.

Passive immunization by injection of antitoxin as soon as possible after a wound has been sustained was first introduced on a large scale in the war of 1914–18 on the Western Front. As a result the incidence of tetanus fell from 9 to 1.4 per 1,000 in three months in 1914, and later in the war it was reduced still further partly by increasing the initial prophylactic dose and repeating it at weekly intervals after severe and heavily infected wounds. Ever since then this method has been used in civil life, but, although the incidence of tetanus has been considerably reduced thereby, many cases still occur which might be prevented. The reasons for this are several: (1) country people are not yet sufficiently aware of the importance of keeping slight wounds clean; (2) some wounds which cause tetanus are not considered sufficiently severe to show to a doctor; (3) others which receive medical attention are not considered severe enough to merit prophylactic antitoxin; (4) prophylactic antitoxin is given, but the dose is too small or not repeated even though the wound is severe or heavily infected, and so modified tetanus develops; and (5) tetanus occasionally follows wounds in which the possibility could not reasonably be suspected or no wound at all, and no antitoxin is given.

Passive immunization could give better results only if the type of wound likely to cause tetanus were more generally appreciated by doctors. One reason for the omission of prophylactic injections may be that most medical students are trained in large cities where tetanus is almost unknown, so that they do not have the salutary experience of seeing the actual disease to impress on them the impor-

tance of prevention, or of seeing the type of wound in the type of person who would be likely to develop tetanus.

After every severe wound, and after every wound of the type described as likely to cause tetanus, 3,000–5,000 I.U., according to the severity, should be injected intramuscularly as soon as possible, and this should be repeated at weekly intervals if chronic suppuration continues, or before further operation. To guard against reactions to horse serum in allergic subjects, or those who have had previous antitoxin, a solution of 1:1,000 adrenaline should be kept at hand and 0.5 ml. injected if required. With care on the above lines it is possible that the incidence might be reduced still further, but many cases would inevitably slip through the net of passive immunization.

Active Immunization

Ramon and Zoeller showed that active immunization against tetanus could be produced by injection of formolized toxin, called "toxoid," and a modification of this method was used and perfected during the war of 1939–45.

To produce immunity two injections of 1 ml. were given at an interval of not less than six weeks to soldiers before they went on active service and a further similar injection once a year while serving. In the British Army an injection of prophylactic antitoxin was also given directly a man was wounded, but in the American Army a further injection of toxoid. The results by both methods were wholly satisfactory, and tetanus was practically stamped out.

While it is true that active immunization of the whole civilian population would eliminate tetanus, its practical application presents economic difficulties, for it would be a heavy undertaking to prevent the comparatively small number of cases which do occur. Conybeare and Logan have suggested that active immunization would be justifiable and practical for schoolchildren at the age of entry in rural districts, and Boyd has recommended it for agricultural workers, grooms, and those exposed to occupational risk of infection. Even limited application of active immunization on these lines would undoubtedly do more to eliminate tetanus than anything else.

Classical Symptoms and Signs

To understand the clinical picture of tetanus it is essential to have a clear idea of the march of the disease and to appreciate that it follows the same sequence whether it is mild or severe. The difference is that in mild cases the march is slow and in severe ones it is rapid. Symptoms first appear from two days to several weeks after injury. The longer the incubation period the milder the attack.

The presenting symptoms are so important for early diagnosis that they will be considered first. In a few cases vague prodromal symptoms which are not diagnostic may occur for twenty-four hours. These include a feeling of nervousness, unaccountable weariness, fleeting pains in the back and limbs, irritability, muscular twitchings, and malaise. Much the most important early symptom which is present in about 90% and should immediately suggest the diagnosis of tetanus is painless stiffness of the jaw or trismus. This is produced by tonic spasm of the masseters, so that the patient experiences difficulty in opening his mouth and masticating food. It is sometimes accompanied by difficulty in swallowing, and occasionally this is the first symptom. At this stage, too, a peculiar facial expression appears—the risus sardonicus. In this the corners of the mouth are drawn upwards and backwards and the forehead wrinkled transversely, the effect becoming more marked when the patient attempts to open his mouth. At the same time, or shortly after, the tonic rigidity spreads to the neck and spine and muscles of the trunk. The spine is arched backwards in the position called opisthotonos, and the abdominal muscles are affected with board-like but painless rigidity. This is usually so marked that when the patient is lying on a flat bed the hand can be passed easily under the lumbar arch—a very useful confirmatory sign. The tonic rigidity can often be increased by manipulation of the limbs or making the patient try to sit up or open his mouth, but the limbs usually remain relatively relaxed. Other presenting symptoms and signs are local tetanus and cranial nerve palsies. Local tetanus consists in slight pain and stiffness in the injured limb and may be the very first symptom. It occurs only in very chronic cases with a long incubation period—usually in those who have been incompletely protected by passive immunization. Its presence heralds a mild attack, provided that treatment is given without delay. Cranial nerve palsies in which usually the 3rd, 4th, or 7th cranial nerves are affected, giving rise to diplopia or unilateral facial weakness of the lower motor neurone type, may be the presenting symptom following wounds of the head and neck. This, too, is probably a form of local tetanus, and the prognosis is also good, provided the treatment is given without delay. Both local tetanus and cranial nerve palsies are accompanied or followed by trismus and generalized tonic rigidity, and the subsequent course is similar.

Progress

Following the initial symptoms tonic rigidity persists throughout the illness until death or recovery. In severe cases it reaches its maximum in a few days; in mild chronic cases it comes on more slowly and passes off gradually after three to six weeks. It is not in itself dangerous, although it limits respiratory movements to some extent. With the increase of tonic rigidity there is an increase in reflex excitability which is shown by increased tone on manipulation or attempted movement. This reflex excitability is the prelude to reflex spasms or convulsions. In very severe cases these first appear about 24 hours after the first appearance of trismus. When a reflex spasm occurs the whole body suddenly becomes rigid; the jaws are tightly clenched; the neck and trunk are arched backwards, the limbs extended, and respiration may be stopped. Such an attack may last from a few seconds to three or four minutes, and the patient foams at the mouth and becomes cyanosed. To begin with these attacks are brought on by external stimuli, such as an attempt to move or drink, noise, or bright light, and they are mild and of short duration. Later they become more violent, of longer duration, and occur spontaneously and with greater frequency. The longer their onset is delayed the better the prognosis. If they are occurring within 48 hours of the onset of trismus the prognosis is bad, and the patient is unlikely to recover. If they are delayed for three days or more the prognosis is relatively good, and the longer they are delayed the better the prognosis. In a severe case when they are established in less than 48 hours death usually occurs within six days. In less severe cases which survive they may continue for any period up to three weeks. After they have ceased, the residual tonic rigidity gradually passes off. Reflex spasms are an indication that the disease is severe, and they are dangerous in that they exhaust the patient, predispose to aspiration pneumonia, and may kill by prolonged respiratory spasm. Tonic rigidity alone is harmless, provided that sufficient antitoxin has been given.

In mild or medium cases the pulse rate is only slightly raised except during reflex spasms, and the temperature remains normal unless some intercurrent infection such as pneumonia develops. In fatal cases terminal hyperpyrexia to 105–108° F. (40.6–42.2° C.) often occurs a few hours before death. Pneumonia is the most frequent and dangerous complication and should always be watched for, and retention of urine is occasionally troublesome.

Diagnosis

The onset of painless stiffness of the jaw in the presence of a recent wound or septic infection of the hands, feet, or head should always suggest the possibility of lockjaw. The characteristic facial expression, stiffness, and arching of the lumbar spine and painless rigidity of the abdomen made worse by manipulation are additional evidence. Local tetanus involving a limb has to be distinguished from fibrositis, neuritis, and local bone or joint lesions; cranial nerve palsies from Bell's palsy, polio-encephalitis, or tuberculous

meningitis. Local lesions of the mouth or throat, such as an impacted wisdom tooth or peritonsillar abscess, although they may cause difficulty in opening the mouth, are painful and can usually be distinguished from true trismus on careful examination. The abdominal rigidity of tetanus has simulated that due to acute abdominal conditions, but the absence of tenderness and presence of trismus should prevent this mistake. At a later stage reflex spasms, accompanied as they are by severe trismus and opisthotonos, are characteristic, but occasionally they have to be distinguished from other causes of fits such as meningitis, encephalitis, epilepsy, and hysteria, and the convulsions of strychnine poisoning are similar except that they do not cause trismus.

The diagnosis of tetanus is essentially clinical, and special investigations are of little value. Lumbar puncture should be avoided except in cases of real doubt. The isolation of the organism from the wound is difficult, often impossible, and too slow to be relied on.

Treatment

This is best considered under four headings: (1) antitoxin and wound toilet; (2) prevention of intercurrent infection; (3) sedation and control of reflex convulsions; and (4) nursing, feeding, and general management.

The aim of giving antitoxin in tetanus is to prevent further absorption of toxin from the wound and to neutralize any toxin in the tissues or circulation before it can reach the nerve cells. If this can be given before a lethal dose has reached the nervous system the patient's life may be saved. To this end a large dose of 200,000 I.U. should be given, preferably intravenously, at the earliest possible moment. If the whole of this dose is not available when the patient is first seen a smaller dose should be given and the rest as soon as possible. A smaller dose given early is probably more effective than a larger dose some hours later. In patients with slight wounds it is unnecessary to give further antitoxin after the single large initial dose, but with severe infected wounds 50,000 units should be given intramuscularly once a week until healing has occurred. This is hardly ever necessary after civilian wounds. Nothing is gained by giving intrathecal antitoxin, and lumbar puncture is liable to excite spasms.

When antitoxin has been given the wound should receive appropriate treatment. Broadly the aim should be to convert an anaerobic into an aerobic infection, with the minimum disturbance of tissues, by thorough drainage and removal of necrotic tissue and foreign bodies.

One of the great risks of tetanus is secondary lung infection. As a prophylactic measure against this 500,000 units of penicillin should be given daily from the outset, and if infection develops in spite of this other appropriate antibiotics may be necessary.

It cannot be too strongly emphasized that the control of reflex convulsions by sedatives and relaxants is only symptomatic treatment. Complete control has little effect in prolonging life in a patient who has already absorbed a lethal dose of toxin. The aim should be to control the severe spasms which exhaust and are dangerous, without depressing respiration so much that the risk of chest complications is increased. Tonic rigidity alone is relatively harmless and can be left alone. In the early stages or in mild cases slight reflex excitability is best treated by large doses of ordinary sedatives such as potassium bromide, chloral, or phenobarbitone. For reflex convulsions bromethol is the drug of choice, but at present is difficult to obtain. This is given rectally as for basal anaesthesia in doses of from 0.07 to 0.1 ml. per kg. of body weight (estimated) twice or even three times daily in severe cases. As an alternative paraldehyde may be given rectally in normal saline in doses of 30 minims per stone of body weight (0.25 ml. per kilo.) two or three times daily or in one-quarter of this dose intramuscularly. Mephenesin antagonizes the convulsions produced by strychnine, probably by depressing reflex activity in the spinal cord, and has been favourably reported on in tetanus. It may be given either intramuscularly or orally in doses of 0.5 to 1 g. for an adult, repeated every few hours according to the effect produced. Opinions vary as to which route is better, but it seems to be relatively more effective in mild than in severe cases. Tubocurarine appears to be liable to excite respiratory spasm and is dangerous. In using sedatives and relaxants in tetanus the first dose should be on the small side and the increment judged by the response.

Because reflex convulsions are excited by stimuli of all kinds tetanus patients should be nursed as quietly as possible in a darkened room. All manipulation such as feeding and giving injections should be done while the patient is most deeply under the influence of sedatives. Nourishing fluid feeds should be given as regularly as possible, and a special nurse is essential in severe cases. When trismus is severe nasal feeding is necessary and intravenous fluids may be required. The mouth should be kept as clean as possible to lessen the risk of aspiration pneumonia, and cyanosis controlled by warmed nasal oxygen. Good nursing may have great influence in turning the scales in borderline cases.

Prognosis

In assessing prognosis the factors which have to be considered are whether passive immunization has been given, the length of the "incubation period," the length of the "period of onset," the severity and site of the wound, the violence of the spasms, the age and physique of the patient, and the presence of intercurrent disease. The "incubation period" is the length of time between the receipt of the wound and the first symptom, which is usually trismus. If infection with *Cl. tetani* has occurred some time after the wound was received this may be shorter than it appears, and therefore misleading. An incubation period of less than seven days means a bad prognosis, but when more than 10 days it is relatively good. When the "period of onset" is less than 48 hours the chances of recovery are slight, but when more than three days relatively good, and they improve with every day convulsions are delayed. If prophylactic antitoxin has been given the attack is usually mild. A severe or heavily infected wound makes the prognosis worse, and it is bad in infants or the aged or those enfeebled by intercurrent disease. The best prognostic yardstick is the period of onset, and this should always be used in assessing the result of any new form of treatment.

It will be seen that tetanus still presents many practical problems in prevention, diagnosis, and treatment. The ideal relaxant has yet to be found, and there is no specific remedy against toxin in the nervous system. The paradox remains that, although preventable, tetanus still occurs in civilian practice. Notification with details of age, sex, occupation, type of wound, and whether active immunization had been given might yield useful data which would make it easier to apply active immunization to certain limited sections of the population.

Next Refresher Course Article.—"Antenatal Care," by Professor W. C. W. Nixon.

A special programme of health education by World Health Organization teams was recently carried out under the auspices of the Egyptian Government in an isolated village in Upper Egypt (*Chron. Wld Hlth Org.*, 1952, **6**, 355). Here a venereal disease control campaign included a complete serological survey of the population of about 9,000 persons and treatment with penicillin of all infected persons and their contacts. Social workers had the task of visiting homes and obtaining the co-operation of village people. Though there had never before been a public meeting for women in the village the team was successful in arranging shows of films and other meetings for them. While blood samples were being taken a rumour went round the village that the blood was being used in the manufacture of certain beverages, but it was successfully dispelled. In the end about 85% of the population submitted to blood tests.

THE ELDERLY AMPUTEE

BY

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Since the advent of the National Health Service the Ministry of Pensions Limb Service has been called upon to treat large numbers of elderly patients, and it was therefore felt that a more detailed study of the results obtained by current methods would be of value and perhaps form a guide to the minutiae of technique and selection in future.

At the inception of the N.H.S. the experience of the Limb Service in the rehabilitation of elderly patients was not extensive, the technique of rehabilitation having been evolved primarily in relation to active ex-Service men. This technique had, however, met with success, and we were encouraged to adopt the same methods, modified only in so far as the programme was adapted to the physical capacity of the higher age groups and the more enfeebled.

Enough time has now elapsed to assess results in respect of the first 6,000 N.H.S. patients accepted for prosthetic treatment at Roehampton. Of these, 344 were "primary" cases—that is, patients who had not yet worn a prosthesis—aged 65 or more, representing some 30% of all the primary lower-limb cases received during the same period. It has been estimated that 4,000 to 5,000 major amputations are performed each year in the British Isles in times of peace, so that the Limb Service can expect some 1,350 new elderly patients annually. The wastage from death and intercurrent disease is, of course, considerable, and only a proportion are successfully equipped with prostheses; but elderly patients requiring continued supervision by the Limb Service throughout the years cannot be expected to be less than 5,000 to 6,000 at any given time.

Technique

The technique adopted in the treatment of this age group has followed the same general plan as that used in the past. Patients are seen as out-patients in the limb centre as soon as possible after reference from hospital. There seems to be no general decision concerning the stage at which patients should be referred. Some hospitals like their cases to be seen by the limb surgeon at an early stage, while others wait until the patient has been discharged to his home.

At first the limb surgeon makes a local and general examination and assesses the capabilities. If further stump or general treatment is indicated he will normally refer the patient back to his hospital with suitable recommendations, unless he feels that the special experience of the Roehampton staff is required. At the earliest possible stage a pylon is ordered for thigh cases, while below-knee cases normally are fitted direct with the permanent prosthesis. The pylons now used are provided with "durestos" sockets (Scales, 1950), and are very light. They can be made in a very short time, and rehabilitation can begin at an early date and so promote morale. It is found that many patients referred to this centre have not persisted with stump exercises and bandaging, the details of which technique have been published by the Ministry of Pensions (1951). Omission of this treatment, or failure to persist in it, results in a flabby stump with terminal oedema and general debility with lack of muscular tone, and in delays and difficulties in limb-training which are in some cases insuperable.

Training in walking is started as soon as possible after delivery of the pylon. We find it better for morale if this is carried out by daily attendances on an out-patient basis, and only those who have too far to travel or have complicating factors are admitted to the hospital. The training consists of individual balancing and walking exercises between handrails, progressing to walking with sticks, stair-climbing, walking on slopes and cambers, etc., and instruction in meeting all the ordinary needs of existence. In conjunction with this, group therapy is employed in the form of suitably modified remedial exercises designed to promote general improvement in muscle tone, to improve reactions, and to stimulate morale. The training is continued until the patient is fully independent or until no further progress can be made. Thus the single below-knee amputee may have two weeks' and the double-thigh subject four or more weeks' training.

After training, the patient is kept under observation by a follow-up, and the permanent prosthesis is prescribed when function merits it. Further training is given after delivery of the permanent prosthesis.

Results

An attempt has been made to assess results obtained in the 344 cases under review in relation to the age and sex of the patient, the site of amputation, the cause of amputation, and the presence or absence of complications. Rehabilitation was regarded as successful in 171 (49.7%). No very exacting criteria have been taken, but cases were considered to be successful if appreciable and regular daily use has been made of the prosthesis for a period of not less than six months from completion of fitting and instruction. Failure occurred in 101 cases (29.4%). Death supervened during rehabilitation procedures or within six months of completion in 31 cases (9%). Fitting was not attempted in 16 cases (4.6%), the result remains uncertain in 5 cases (1.5%), and follow-up has failed to trace 20 patients (5.8%).

TABLE I.—*Results in Relation to Age*

Age:	85+	80–4	75–9	70–4	65–9	Total
S ..	3 (50%)	7 (29·3%)	31 (41·3%)	54 (52·4%)	76 (55·9%)	171 (49·7)
F ..	2 (33·3%)	9 (37·5%)	26 (34·7%)	28 (27·2%)	36 (26·5%)	101 (29·4%)
D ..	0	2 (8·3%)	9 (12%)	9 (8·7%)	11 (8·1%)	31 (9·0%)
NT..	0	2 (8·3%)	5 (6·7%)	7 (6·8%)	6 (4·4%)	20 (5·8%)
NA	1 (16·7%)	2 (8·3%)	4 (5·3%)	3 (2·9%)	6 (4·4%)	16 (4·6%)
U ..	0	2 (8·3%)	0	2 (2·0%)	1 (0·7%)	5 (1·5%)
Total	6 (1·7%)	24 (7·0%)	75 (21·8%)	103 (29·9%)	136 (39·6%)	344

S=Satisfactory. F=Failure. D=Death. NT=Not traced. NA=Not attempted. U=Uncertain.

Table I shows, as would be expected, an increasing failure rate with age. The high proportion of successes in the oldest group is probably not significant, owing to the small numbers involved, except to show that age itself is no bar to successful rehabilitation. The oldest patient to be treated was a woman born in 1860 who had had the right leg amputated above the knee when she was 5 years old but had never worn a prosthesis. To this extent she was perhaps not strictly a primary case, as she had not recently had a debilitating illness or undergone major surgery. She has been included, however, on the ground that it was her first attempt with a prosthesis. She was fitted with a pylon in November, 1948, and with an articulated prosthesis seven months later. She made uninterrupted progress despite domestic difficulties, and when last seen in September, 1951, she was "making better use of her leg than many half her age." At the other end of the scale six of the youngest patients were so debilitated that limb-fitting was not attempted, and over 25% have failed to learn to manage a prosthesis. The oldest double-thigh amputee to make successful use of prostheses was 81.

The incidence of failure has been higher in females. Table II shows the relative figures. There were approximately twice as many males as females in the series.

TABLE II.—*Results in Relation to Sex Distribution*

	S	F	D	NT	NA	U	Total
Male ..	119 (52·1%)	55 (24·2%)	24 (10·5%)	13 (5·7%)	12 (5·3%)	5 (2·2%)	228
Female	52 (44·8%)	46 (39·7%)	7 (6·0%)	7 (6·0%)	4 (3·5%)	0	116

The death rate was appreciably higher amongst the males. It may be that they approached their rehabilitation with greater determination to overcome their disablement, in many cases possibly through a feeling of economic compulsion, which could explain the higher success rate at the cost of shortening life in some of them. The numbers are not large enough for us to draw more than tentative deductions on this score, particularly as the death rate in general in this age group is higher in males.

TABLE III.—*Site of Amputation*

	Single A.K.	Single Thro. K.	Single B.K.	Double A.K.	One A.K. One B.K.	Double B.K.	Upper Limb	Total
S ..	118 (49·4%)	5 (62·5%)	26 (57·8%)	14 (36·8%)	3 (33·3%)	3 (100%)	2 (100%)	17
F ..	73 (30·5%)	2 (25%)	9 (20%)	16 (42·1%)	1 (11·1%)	0	0	101
D ..	21 (8·8%)	0	5 (11·1%)	3 (7·9%)	2 (22·2%)	0	0	31
NT..	11 (4·6%)	0	5 (11·1%)	3 (7·9%)	1 (11·1%)	0	0	20
NA	12 (5·0%)	0	0	2 (5·3%)	2 (22·2%)	0	0	16
U ..	4 (1·7%)	1 (12·5%)	0	0	0	0	0	5
Total	239	8	45	38	9	3	2	

The preservation of the knee-joint is, of course, normally an advantage. However, the low success rate among those who have suffered double amputation—one above and one below the knee—the high death rate, and the high proportion for whom limb-fitting could be attempted (Table III), support the apparently paradoxical view held by me that in patients of this age rehabilitation, at least to a measure of independence, has been more readily effected among those who have had a double amputation at or above the knee. This is in direct relationship with the technique employed in the latter case, because initial rehabilitation is undertaken on short pylons, on which the patient is kept as near the ground as is permitted by the longer of the two stumps, and effort is minimized. A recent development of this technique, not included in this series, is the addition of rocker bases to the short pylon, which further reduce the expenditure of effort. The results of this method are most promising but it would be premature to give figures at this stage. (Note: The supply and use of short pylons has been regarded as a successful outcome in the double above-knee cases, although only five of them progressed to full-length articulated limbs within the period of review.)

Disarticulation at the Knee

Although the numbers are small, it is interesting to note the high success rate of disarticulation at the knee. (This includes two Stokes–Gritti amputations, of which one failed.) The success of these cases tends to confirm the impression gained that such patients learn to walk more readily and gain balance and confidence more quickly than those with the conventional above-knee amputation. This is probably because, with a disarticulation at the knee, end-bearing can often be tolerated, thus permitting the axis of the body weight to be borne through the femur instead of through the ischium, and requiring less readjustment. It is necessary to provide a somewhat more cumbersome prosthesis for the disarticulation case owing to the bulbous extremity of the stump, and it is probable that the gait can never be so good as that obtained with the prosthesis designed for the ideal stump, but it is felt that for the elderly these disadvantages are outweighed by the relative ease of the early rehabilitation and, above all, by the fact that such an operation is the simplest one and is attended by the minimum of shock.

In only one of the cases (the one classified as uncertain) was there any breakdown of the stump, and it would seem that disarticulation could be adopted with advantage for many more patients in the age group under consideration. The Stokes–Gritti stump has never proved very satisfactory among ex-Service men from the limb-fitting point of view; end-bearing is seldom tolerated, and the terminal soft tissues are prone to circulatory deficiency, possibly owing to the fact that the flaps may have been taken too high to obtain advantage of the anastomosis round the knee. There seems no reason to expect better results in the higher age group than in the younger patients we have seen in the past, and the bone section involved would cause the very surgical shock which one wishes to avoid. We therefore do not see any place for the Stokes–Gritti amputation or any other modification of the classical disarticulation at the knee for the elderly patient.

Cause of Amputation

The most significant fact, as shown in Table IV, is that diabetics have relatively poor prognosis with regard to both rehabilitation and survival. As might be expected, in the acute pyogenic and traumatic groups the success rate is high. This is probably because they have not suffered from prolonged debilitating illness. The presence or absence of concomitant disease or disablement is of more direct prognostic significance.

TABLE IV.—*Cause of Amputation*

	S	F	D	NT	NA	U	Total
Diabetes ..	20 (34·5%)	22 (38·0%)	9 (15·5%)	4 (6·9%)	3 (5·1%)	0	58
Embolism ..	0	1 (50%)	1 (50%)	0	0	0	2
Thrombosis ..	4 (33·3%)	4 (33·3%)	1 (8·3%)	1 (8·3%)	1 (8·3%)	1 (8·3%)	12
Raynaud's disease	2 (100%)	0	0	0	0	0	2
Other forms of gangrene	90 (50·6%)	55 (30·9%)	12 (6·7%)	11 (6·2%)	8 (4·5%)	2 (1·1%)	178
Ulceration ..	24 (61·6%)	8 (20·5%)	2 (5·1%)	1 (2·6%)	2 (5·1%)	2 (5·1%)	39
Neoplasm ..	10 (55·6%)	4 (22·2%)	4 (22·2%)	0	0	0	18
Trauma ..	11 (61·1%)	3 (16·7%)	1 (5·6%)	2 (11·1%)	1 (5·6%)	0	18
Pyogenic infection	6 (75%)	1 (12·5%)	0	1 (12·5%)	0	0	8
Tuberculosis ..	1 (33·3%)	2 (66·7%)	0	0	0	0	3
Aneurysm ..	2 (50%)	0	1 (25%)	0	1 (25%)	0	4
Elephantiasis ..	1 (50%)	1 (50%)	0	0	0	0	2
Total ..	171	101	31	20	16	5	344

Complications

The complications (Table V) were in the main cardiovascular and respiratory, and disorders of locomotion. The latter include disabilities of the upper limbs, owing to the fact that these patients have at least to learn to walk as quadrupeds. Specific complications, together with numbers of cases exhibiting each complication, are shown in

TABLE V.—*Complications*

	S	F	D	NT	NA	U	Total
Complications present	81 (40·1%)	66 (32·7%)	20 (9·9%)	14 (6·9%)	16 (7·9%)	5 (2·5%)	202
Complications absent	90 (63·4%)	35 (24·7%)	11 (7·7%)	6	0	0	142

Table VI. It will be appreciated that two or more complications may have been coexistent in individual cases. The figures emphasize the importance of defects of the contralateral leg, the arms, vision, heart disease, and deafness.

TABLE VI.—*Specific Complications*

	Total	Successful	
		No.	%
Defects of contralateral leg	72	26	36
Defects of stump	56	26	46
Gross obesity	31	16	52
Hernia and hydrocele	18	9	50
Myocardial disease	17	5	29
Defects of upper limbs	15	4	27
Chronic bronchitis, with dyspnoea on exertion	13	6	46
Defective vision	11	2	18
Intercurrent hemiplegia	9	3	33
Deafness	8	2	25
Cerebral arteriosclerosis	7	3	43
Psychological overlay	4	1	25
Dermatitis (general)	4	1	25
Previously treated neoplasm in breast	2	2	100
Tabes dorsalis	2	2	100
Intercurrent prostatectomy	2	1	50
Bedsore	2	—	—
Scoliosis, peripheral neuritis	1	—	—
Prolapsus uteri	1	—	—

The last of these is interesting, and its inclusion among the complications is probably explained by the fact that the deaf person retires into himself and is difficult to bring into group therapy and into the atmosphere of optimism one can cultivate in his more fortunate fellows. Obesity has been less of a handicap than might have been expected.

Discussion

The results in these cases show that no single complication encountered can be regarded as an absolute contraindication to limb-fitting. On the other hand, one cannot simply regard the elderly amputee as having a stump for which all that is required is to fit a prosthesis to enable him to walk. On the contrary, the stump is by no means the most important part of the problem. A comprehensive examination must be made of the patient's entire physical and mental make-up, and suitable treatment of any concomitant disability instituted in conjunction with prosthetic rehabilitation.

The complicating factors are, in fact, wider even than this. The environment to which the patient returns on discharge is of vital importance. We not infrequently see patients who have made good progress and who are discharged from the walking school able to control their prosthesis and to look after themselves fairly well. Yet when we see them on follow-up we find they have hardly worn the prosthesis, and the musculature has lost tone to the extent that they can no longer control it. Inquiry reveals that they live alone, perhaps in an upstairs flat, or it may be that they have simply lacked the incentive to make the effort to persevere. It would seem that here is a problem of welfare which is outside the scope of the Limb Service, and falls more within the province of the social medicine specialist.

Again, we have had to contend with patients who have acquired an unwarranted optimism concerning what can be done for them. They expect to be provided with a prosthesis with which they can walk immediately and without effort. They may be in poor physical condition, and often their stumps may be flabby, neglected, and quite unprepared for wearing a prosthesis. It is impossible to convince some of them that they will not be able to manage a prosthesis other than by letting them try for themselves on a pylon. The effect on morale of the inevitable failure can be imagined. We have known of patients admitting that they had been prevailed upon to accept amputation by the promise of easy function with a prosthesis. The psychological approach from the limb surgeon's point of view is much simplified if a more conservative briefing has been given in the general hospital and the patient has been warned beforehand that he will have a prolonged and strenuous programme before him, but that if he will make the effort he should be able to walk. This programme should be initiated from an early date and maintained throughout by a regime of active physiotherapy, directed not only to the stump but to the whole bodily musculature, together with occupational and diversional therapy suited to the intellectual standard of the individual. The programme can with advantage be phased, each phase having a target which must be attained before the next phase is started (Marjory Warren, 1950, personal communication). This may seem a counsel of perfection unrelated to the pressure on hospital beds in these days, but it is my belief that there would actually be a saving of time, and therefore of beds, if such a programme were in uniform use.

The following brief case histories illustrate some of the points raised.

Case 66.—A married woman aged 68. Double above-knee amputation, the later amputation being performed on December 22, 1948, for gangrene of unspecified nature. She was grossly overweight. W.R. positive; prior to the amputation she had been diagnosed as tabetic. She made uninterrupted progress on short pylons, and, although she did not progress to full-length articulated limbs, she obtained enough function from the short pylons for the result to be regarded as an unqualified success.

Case 69.—A man aged 81. Amputation of right thigh through lesser trochanter following road accident. There was an unreduced congenital dislocation of the left hip. He lives by himself. He learned to manage a "through hip" (tilting table) prosthesis without difficulty, and in spite of his unfavourable home circumstances continued to make good use of it.

Case 223.—A married woman aged 66. Left above-knee amputation as a result of old-standing osteomyelitis. She had generalized seborrhoeic dermatitis, was deaf, and had defective vision (6/60 R. and L.). Despite this, she did well on a pylon and also learned to manage an articulated prosthesis competently. Four months later she was found to have given up the effort and had reverted to a wheelchair existence.

Case 251.—A man aged 69. Right above-knee and left below-knee amputation. Despite his excessive weight he made an uninterrupted and rapid rehabilitation, which was maintained.

The cause of death in the 31 patients who died during or immediately following limb-fitting procedures was as follows: coronary occlusion, six; hypertensive myocardial failure, four; diabetic coma, three; pneumonia, hemiplegia, and secondary carcinomatosis, two each; renal failure in association with diabetes, diabetic gangrene of contralateral leg, senile gangrene of contralateral leg, dissecting aneurysm with renal suppression, and perforated gastric ulcer, one each. In seven cases the cause of death could not be ascertained. Only one death occurred while the patient was actually undergoing fitting of the prosthesis or training in walking; this patient collapsed and died of acute cardiac dilatation in the walking school. He was a hypertensive subject.

In consideration of the fact that all cases in the series were under observation for upwards of a year, the death rate gives no cause for alarm or for modification of policy. It is very doubtful if the effort of limb-fitting had any material effect in shortening life, and, even if it did, the majority of patients would prefer to make the attempt rather than pass the rest of their life in a chair. The manifestly bad risks were not attempted.

Summary

A series of 341 consecutive primary amputees of 65 years or more who have been referred to Roehampton Limb Fitting Centre for a prosthesis has been reviewed.

The results suggest that no single factor will determine the selection of patients suitable for limb fitting, and that an assessment must be made of the entire physical and mental make-up. Age itself is not an adverse factor, and there is no evidence that wearing a prosthetic limb has shortened life significantly.

It is suggested that correct briefing and an energetic and continued physical programme are of inestimable value in preparing patients for wearing a prosthesis.

The subsequent care of the elderly amputee after training in the use of the prosthesis is a problem in social medicine as yet not adequately met.

I am indebted to the Director-General of Medical Services, Ministry of Pensions, for permission to publish this paper. My thanks are also due to Dr. R. Langdale Kelham for advice and help in preparing the text, and to the staff of Roehampton Limb Fitting Centre, in particular to Mr. D. Congalton, senior walking instructor, without whose enthusiasm and untiring efforts many of these patients would never have walked.

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ORDER OF ST. JOHN OF JERUSALEM

The *London Gazette* has announced the following promotions in, and appointments to, the Venerable Order of the Hospital of St. John of Jerusalem:

As Knights: Sir Horace Evans, K.C.V.O., M.D., F.R.C.P., Major-General F. A. Maguire, C.M.G., D.S.O., V.D., M.D., F.R.C.S., Brigadier R. M. Gorssline, D.S.O., M.B., Lieutenant-Colonel E. A. H. Russell, O.B.E., V.D., M.B., Mr. A. Wai Tak Woo, M.B., F.R.C.S., Drs. G. B. Peat and C. A. Verco. *As Dame:* Mrs. Katie Ardill-Brice, O.B.E., M.B. *As Commanders (Brothers):* Colonel T. E. Holland, M.D., Drs. Tseung Fat in, E. H. Lodge, K. C. McGibbon, H. R. Mustard, and W. P. Warner, C.B.E., D.S.C. *As Associate Commander (Brother):* Dr. K. Budeiri. *As Commander (Sister):* Dr. Ella P. Hopgood. *As Officers (Brothers):* Surgeon Rear-Admiral F. H. Nimmo, Brigadier C. W. Nye, O.B.E., E.D., M.B., Colonel W. A. Jones, O.B.E., V.D., M.D., Colonel J. E. Snow, R.A.M.C., Lieutenant-Colonel S. H. Heard, M.B.E., M.R.C.S., L.R.C.P., Major A. S. Lewis, M.D., F.R.C.S., Messrs. D. P. McIntyre, F.R.C.S., H. H. Barnett, M.B., F.R.C.S., A. Perry, O.B.E., M.B., F.R.C.S., C. D. Gossage, O.B.E., M.D., F.R.C.S., W. H. C. Romanis, *M.C.*, M.B., F.R.C.S., Drs. J. K. Thomas, J. Brown, T. P. Eddy, L. G. Blaze, C. H. Drake, G. W. J. Bousfield, P. P. Lynch, W. G. Rich, R. J. Brown, G. D. W. Cameron, E. Dwyer, H. J. Ferrier, J. L. R. Gendron, H. D. Hebb, J. H. A. Paquette, W. S. Stanbury, M.B.E., H. H. C. Fuller, L. M. Comissiong, E. R. B. Murray, G. K. Thornton, J. Prentice, R. McC. Paterson, N. L. Birkett, J. J. du Pre Le Roux, R. S. Steel, H. H. Hurst, and T. C. James. *As Officers (Sisters):* Mrs. Ellen W. M. Shaw, M.R.C.S., L.R.C.P., and Miss Olive S. May, M.R.C.S., L.R.C.P. *As Serving Brothers:* Surgeon Captain E. H. Lee, Captain A. F. McDonald, M.B., Messrs. M. Backwell, M.B., F.R.C.S., D. R. Jennings, M.B., F.R.C.S., Drs. R. G. Sprenger, I. B. McRae, Chang Hoey Chan, C. L. Tessensohn, V. P. Robinson, R. N. Curnow, J. A. Sacco, R. H. Blackburn, W. Isbister, A. Barlow, J. Crook, E. MacD. Fogo, J. A. Mackay, J. J. MacRitchie, A. L. Peers, N. R. Rawson, O.B.E., R. R. Strong, Ll. H. Werden, T. H. N. Whitehurst, O.B.E., E. B. Figueiredo, D. P. K. Jockel, T. K. Abbott, L. W. Fitzmaurice, O.B.E., R. D. K. Levy, P. D. A. Fowler, H. W. Needham, E. T. Meyer, J. D. Allen, C. D. Bateman, R. Swinburn, V. C. Dyring, N. J. Caldwell, and F. W. R. Lukin. *As Associate Serving Brothers:* Drs. A. J. Thumboo, E. B. Israel, R. A. Trope, S. Etzine, and H. Kaye. *As Serving Sisters:* Drs. Sophia M. R. Thomson, Margaret Owens, Winifred I. Robertson, and Marguerite C. MacDonald.

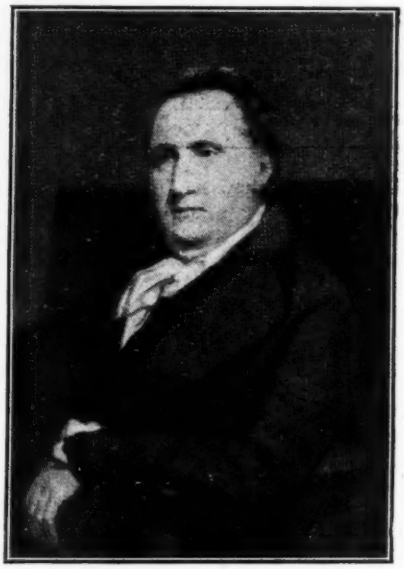
The benefits of a chiropody service to old people are emphasized by Dr. H. J. Rae in the *Health Bulletin* (January, 1953) of the Department of Health for Scotland. For some time the service has been provided for the residents of old people's homes belonging to the Aberdeen Corporation, and other local authorities in Scotland have made similar provision. More recently the scheme has been extended to cover old people in their own homes in Aberdeen. The service is not free, since experience has shown that chiropody treatment given free at out-patient clinics was grossly abused. A charge of 4s. per visit is therefore made, but it may be remitted in whole or in part if circumstances so require.

Nova et Vetera

DR. JAMES GREGORY

NEW LETTER FOUND

James Gregory, who was born in January, 1753, is remembered to-day only through the powder which bears his name, although in his lifetime he was a most striking figure in the Edinburgh School of Medicine. He graduated M.D. at Edinburgh in 1774 and then spent some time under Gaubius at Leyden. His father, John Gregory (1724–73), occupied the chair of practice of medicine at Edinburgh from 1766 until his death. For 20 years previously Robert Whytt, professor of the institutes of medicine, had been the actual professor of the practice of medicine, and in 1769 his successor, William Cullen, petitioned the authorities to appoint him and John Gregory joint professors of medicine, so that each should teach in alternate sessions the theory and the practice of medicine. When John died, James Gregory was still a student. Cullen continued as professor of practice of medicine, and the chair thus made vacant was not filled until June 19, 1776, when James was elected professor of the institutes of medicine, becoming the fifth member of the Gregory family to occupy a professorial chair at Edinburgh. Soon afterwards he published his textbook, *Conspectus Medicinae Theoreticae ad Usum Academicum.* In 1792 he succeeded Cullen to the chair of practice of medicine. He was an accomplished Latin scholar, a great physician, and a brilliant and witty lecturer. His teaching enhanced the reputation of the Edinburgh school over a long period, and his reputation was second only to that of Cullen. He published a set of literary and philosophical essays in 1792. Gregory was a friend of Robert Burns, and Raeburn painted his portrait in 1798; a part of it is reproduced here.* He died in 1821.



Obviating Costiveness

A letter, reproduced below, written by Gregory to an unknown correspondent has recently been brought to light, and the bicentenary of Gregory's birth is an appropriate occasion for its publication. The letter was discovered among papers in the possession of Captain Sir James Paget, Bt., R.N., of Ballater, a grandson of Sir James Paget, the distinguished surgeon, and it has been presented to the British Medical Association.

St. Andrew's Square
Wed: Night 22 Jan: 1817.

Sir,

Inclosed I send you a Receipt for the same kind of Laxative Pills, which by Dr. Macfarlane's advice you have been using of

*The illustration is taken from the reproduction of the Raeburn portrait of Dr. James Gregory in *History of Scottish Medicine* by John D. Comrie, 2nd edition, vol. 2, 1932, by kind permission of the publishers, the Wellcome Historical Medical Museum. The original is in the possession of Sir Ian Forbes-Leith, Bt.

late; and which have agreed so well with you as not only to have most effectually obviated Costiveness, but *almost* to have cured your Stomach Complaints: thereby shewing clearly that these Complaints proceeded solely, or chiefly, from Costiveness.

You ought certainly to continue to take them, more or less frequently as you shall find necessary to keep your Body regularly open: or at least to prevent you from ever going *Two Days* successively without a Stool. You need have no fear of any bad consequences from them, if you take them, even every night at Bed-time, in such moderate quantity as to procure you *one easy* Stool next day. If *one Pill* has *this Effect*, it would be needless, and wrong, to take *more* of them. But if one of them shall prove insufficient to produce that Effect, you ought to take *Two*, or *Three*, of them: and if the *Evening Dose* shall not have operated by 9 o'clock next morning (or your usual time of going to Stool) you should repeat it *then*, and every Three or Four hours afterwards till the Pills begin to operate.

No doubt it will be better for you, if you can, *wholly* or partly, obviate Costiveness, by *proper Diet*; so as not to need to take the Pills so often as every night: for example, if you shall not need to take them oftener than every *alternate* night; or *twice a week*, or only *once* a week. Very possibly, you will, in a short time, *acquire such a habit* of a regularly open body, that you may not need to take the Pills even once in many weeks, or months.

The *Diet* that will *help* most to keep your Body regularly open, is one composed chiefly of *plain fresh Meat* or *white* (sea) Fish, with a *large proportion* of *vegetable Food:* well fermented, *stale* (not new: baked) Bread, good Scotch Broth, *well boiled* Garden Stuff (Turnips, Carrots, Spinach, Brocoli, Collyflower, Peas, Beans, Leeks, Onion, &c.) and *ripe* Fruit; or stewed Fruit, such as Apples, Pears, or Prunes:—and, for drinks, *fresh mild Malt Liquor:* if this do not particularly disagree with your Stomach.—You ought certainly to abstain from all Fat, salted, smoaked, hardened, and high Seasoned Meat or Fish; such as Ham, Bacon, Tongue, Pork, Salmon, Herring, Stock Fish, Curries, Ragouts, rich Soups, Pastry, Cheese, Butter Sauces; or indeed much Butter in any shape.

Very possibly, on *first trying* a good proportion of such Laxative Vegetable Food as I recommend to you, you will feel some uneasyness about your Stomach, perhaps Heartburn or other Pain: but this may easily be removed by the use of *Henry's Calcined Magnesia:* the best preparation of that excellent Medicine; which, without any Physician's formal prescription, you may get at any good Apothecary's Shop, by its proper name. *One* or *Two* large Tea spoonfulls of it mixed in a Tea Cupfull of cold Water, or of Peppermint Water, will effectually and very speedily correct any Acidity, and remove any pain in your Stomach. The Magnesia will also *contribute* to keep your body open.

It may happen, however, that there shall be *Acidity* and *Pain* in your Stomach, while at the same time your body is sufficiently open, or too open. In this Case, you ought to take, *not* the *Magnesia*, but instead of it, the *Alcaline Powder*; for which I inclose a Receipt, subjoined to that for the Pills. This Powder will correct Acidity and relieve Pain in the Stomach, just as certainly and speedily as the Magnesia would do: and will *not* be laxative. The Dose of it should be *one moderate (not a heaped)* Tea spoonfull: and it ought to be taken *dissolved* in a large Tea cupfull of cold Water or of Peppermint Water.

As you mentioned to me your intention of going soon to England, I have given you, as I promised I should do, the Receipt for the Laxative Pills, by the Name which is given to that *Composition* all over England.—If you wish for a supply of them in Scotland, you may get it from any good Apothecary by the name of the *Colocynth Pills* or the *Pilulæ Aloes cum Colocynthide:* And you will know at once if the Apothecary give you the right kind, by its smelling finely of *Cloves*.—It is the only kind of Pill which in the Edin. Dispensatory is directed to be made up with the addition of Oil of Cloves.

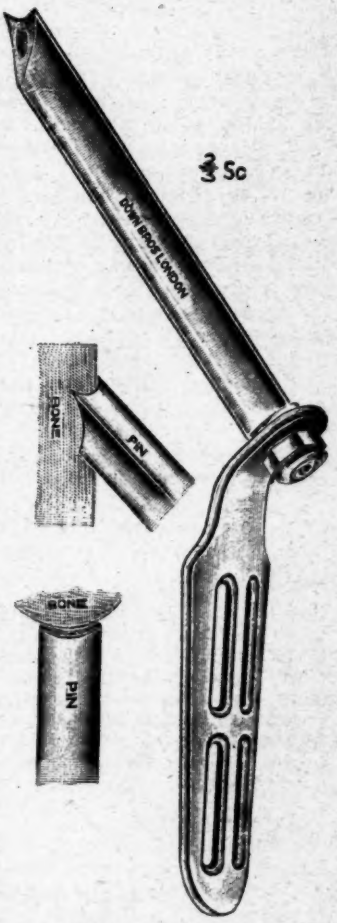
I have the honour to be,
Sir,
your most obedient Servant,
J. Gregory, M.D.

According to the *New York Times* the Toni Company, the specialists in hair cosmetics, has recently opened a large laboratory in Chicago to study hair. Much is already known about human hair, and some of its properties are surprising. The Toni workers are reported as saying that it has a breaking strength of about 6,000 lb. per sq. in. (422 kg. per sq. cm.), half the breaking strength of iron. Dry hair can be stretched 20% without breaking, and wet hair even more. On an average hair grows about half an inch (1.25 cm.) a month.

Preparations and Appliances

NAIL FOR TROCHANTERIC FRACTURES

Mr. DAVID F. THOMAS, consultant orthopaedic surgeon, Scunthorpe War Memorial and Lincoln County Hospitals, writes: In internal fixation of low trochanteric fractures of the femur the nail must be introduced at a lower level than in the treatment of transcervical fractures. The angle of impact of the nail on the surface of the outer cortex is therefore much more acute in the former case than in the latter. The more acute the angle of impact the smaller is the initial contact between the tip of the nail and the bone and the more likely is the nail to slip up on the surface of the cortex rather than to penetrate it. Sometimes it may slide upwards only a short amount, and it may then penetrate the cortex. If it does this it is likely to bend the guide wire at the level of the outer cortex, with the result that the guide wire is carried in. These difficulties can be overcome by thinning down the cortex at the site of entry of the nail. By this means the nail penetrates easily and does not tend to slide or jump, but the grip of the nail in the outer fragment is jeopardized.



It is preferable to remodel the head of the nail (see illustration) so that when entering at an acute angle the face of the end lies flush with the femoral cortex. The effect of this can be enhanced by pointing the ends of the fins so that they stick into the cortex, and by shaping the contour of the face of the end so that it fits the circumference of the femoral shaft.

I have not found that the use of the trifin osteotome is the answer to the problem described here. It will guide the point of the nail only if one makes a good deep cut through the cortex, and I have found that when one does that there is sometimes difficulty in withdrawing the osteotome, with the risk of disturbing the position of the fracture. On the other hand, if the osteotome is made to penetrate only a short distance in the cortex the cut may not be enough to guide the nail inserted at an acute angle, as in this case only one fin of the nail enters the cortex at the beginning of the nail's traverse.

In most of my cases of trochanteric fractures I have used the McKee apparatus for internal fixation. I much prefer, if possible, to keep the outer fragment intact, so that the nail exerts a firm grip directly on that fragment in addition to the grip which it exerts on it through the plate. The nail should be as nearly at right angles to the general line of the fracture as it is possible, and therefore, in low trochanteric fractures, a low nail is preferable. A low nail means an acute angle of introduction, and the modification I have described helps to achieve a smooth penetration of the nail at an acute angle. This nail has been made for me by Messrs. Down Bros., to whom my thanks are due.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

The Central Midwives Board and Sir Francis Champneys

SIR,—In the reports of the festivities to celebrate the 50th anniversary of the passing of the first Midwives Act and the birth of the Central Midwives Board, it is surprising to see so little reference to Sir Francis Champneys, who did so much to promote the Bill and was the first chairman of the Central Midwives Board from 1902 until his death in 1930. However great his part in promoting the Bill, and I understand from some of those who worked with him that his was the main driving force behind it, it was his administrative ability, patience, firmness, and tact as chairman of the Central Midwives Board which made possible the implementation of the Act and the development of the great profession of midwives as we know it to-day. Prior to the passing of this Act, midwives, as a whole, were drawn from a poor social class, often quite illiterate, and their training was of the scantiest, while in many instances the handy woman without any training was in charge. The Act of 1902 forbade any woman to attend a confinement unless she was on the Register of the C.M.B., and laid down a period of resident training in a maternity hospital and the passing of an examination for those who aspired to this.

To tide over the period until a new generation of better-trained women was available the old midwives had to be employed, and the first Register consisted of those who had been in practice as midwives for a year before the passing of this Act. Some latitude had to be given, and I think I am right in saying that after January 1, 1905, no woman could be placed on the Register unless she had completed the prescribed training and passed the C.M.B. examination. On this date the first "Inspector of Midwives" appointed by the City of Manchester commenced her duties, and no doubt in other centres also, and by a curious chance I commenced my 3½ years as resident obstetric officer to St. Mary's Hospital, Manchester, on the same date. In this post I had the usual responsibilities of a senior resident for the hundred obstetrical and gynaecological beds in the hospital, and in addition I had complete responsibility for a large home district in which 3,000–4,000 confinements per annum were attended by hospital district midwives, every one of whom was now on the Register by virtue of having been in practice before the passing of the Act. Many of these women had acquired much clinical knowledge and the great majority were devoted to their patients and their work, but, with a few notable exceptions, they were drawn from a poor social class with little education. Some were almost illiterate and incapable of absorbing anything from the course of lectures they had attended, while few of the others understood the meaning of "sepsis" and "antisepsis," and still preferred a little freshly rendered lard as a lubricant. These, I think, were a fair sample of the midwives of the country, and the task of the C.M.B. was to keep the midwifery service of the country functioning. By slow degrees they replaced the worst offenders by newly trained midwives and educated the more intelligent of the old ones to a higher standard of practice.

To have removed from the Register all who failed to conform to modern standards before new ones had been trained would have created chaos; to have been too lenient and weak would have failed to bring home to the profession the necessity of improvement if they were to retain their registration. Above all it was necessary to improve the tests of general education of the candidates, to increase the training and to stiffen the standards of the C.M.B. examinations. Only in this way could a profession be created which would attract candidates from a higher social scale with greater intelligence and better education. That this was done gradually without chaos and with the mimimum of friction was due in no small measure to the firmness, patience, and breadth of vision of the first chairman of the Board, Sir Francis Champneys. With each step a better class of woman was attracted to the service, until now it is one of which the members are justly proud and with its own college.

This indeed is a fitting memorial to the wise guidance of Sir Francis Champneys through the 28 years of his chairmanship. As there can be few, if any, alive to-day who saw at such close quarters the work of the C.M.B. and its chairman, I feel that I must put on record what this service owes to him.—I am, etc.,

Manchester. W. FLETCHER SHAW.

Thiouracil in Toxic Goitre

SIR,—I would like to congratulate Dr. David Douglas and Dr. Agnes T. Kennie on their excellent article on thiouracil for toxic goitre (December 27, 1952, p. 1387). Their final conclusions will be agreed to by most surgeons and by an increasing number of physicians interested in the problem. They did not, however, differentiate between the two types of thyrotoxicosis. In my experience thiouracil has proved to be much more satisfactory in Graves's disease, with small generalized enlargement of the gland. Where thyrotoxicosis is associated with nodularity of the gland, however, the results have not been as encouraging. Indeed, it has now become my practice to use thiouracil only as a pre-operative measure in this type of case.

In the article already referred to it is stated that the mortality from surgery is probably not more than 2%. This figure is considered to be too high. If thyrotoxic symptoms can be controlled satisfactorily in the pre-operative period, which is possible in a large majority of cases, mortality should be under 0.5%. In my own series of cases of over 200 thyroidectomies, there has only been one death. The use of thiouracil was denied to us in this patient because she had had repeated courses over a period of four to five years, and the drug had ceased to be effective. It is probable that had operation been performed at an earlier stage she would have survived the procedure. Regarding the other complications of surgery, there has been no instance of hypoparathyroidism or vocal-cord paralysis in this series. Myxoedema has only occurred following thyroidectomy for Hashimoto's disease, a condition which is not so rare as some authorities would lead us to suppose.

Dr. Douglas and Dr. Kennie stress the difficulties of prolonged pill-swallowing, and I agree with them entirely that this type of therapy tends to produce some degree of neurosis. Also, there is no doubt that thiouracil affects the general health of the patient. They were fortunate not to have any fatalities from agranulocytosis.

In conclusion, it has been my experience that patients who have had prolonged courses of medical treatment, and then subsequently been submitted to thyroidectomy, often wish they had received operation at a much earlier stage in the treatment of their condition.—I am, etc.,

Newcastle-upon-Tyne. DENIS HINDMARSH.

Benefits and Dangers of Butazolidin

SIR,—May we be permitted to comment on your leading article on "butazolidin" (December 27, 1952, p. 1401)? The following observations are offered in no spirit of carping criticism, but only because we feel that they are important at this stage in the investigation of a promising new therapeutic weapon.

The first investigations of butazolidin in the treatment of rheumatic disease were conducted here, and the results presented by one of us (J. P. C.) in a paper read before the Second European Congress of Rheumatology in September, 1951.[1] Subsequently, at the instigation of the American division of Geigy Pharmaceuticals, Kuzell and his colleagues undertook their investigations.

The effect of butazolidin on the E.S.R. and joint swelling is by no means the observation of only one worker, and, indeed, far from being unconfirmed, several of the authors your writer cites report similar findings. Thus Kuzell *et al.*[2] state, "The analgesic properties of phenylbutazone are excellent; particularly in early and acute cases there is a marked decrease in joint swelling and muscle stiffness suggesting a more general anti-rheumatic effect." In the same paper these authors show that the E.S.R, returned to normal in

3 of 29 patients. So, too, Steinbrocker *et al.*[3] report reduction of the E.S.R. in 10 of 117 cases and objective improvement of Grade III* or better in 50% of their patients, while 23% showed "'anti-arthritic' effects of notable degree." Similarly Stephens *et al.*[4] report "marked decrease in swelling in 47 of 115 patients (41%)." These findings may not be "impressive" to your writer, but they do not occur in control groups, and, since there is no reason to suppose them to be inaccurately presented, surely they must be explained.

With regard to the analgesic effect of butazolidin, we have ourselves drawn attention to the fact that performance tests are affected by subjective feelings of improvement, and that they are not to be loosely interpreted. From your leading article it would appear that Steinbrocker and his colleagues demonstrated that butazolidin was in general a more powerful analgesic than salicylates or amidopyrine. It should be made clear that their observations were made on *rheumatic conditions* (rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, etc.). With this we are in entire agreement, but, in addition, our observations are that it is a poor analgesic in conditions other than these; in this we are supported by the experimental findings of Wilhelmi[5 6] and the clinical observations of Hart.[7] The fact that the so-called "new antipyretics" possess analgesic properties and that these are most noticeable in the "rheumatic" states has long attracted our attention and is precisely what led us to test butazolidin originally.

Comment and opinion regarding the use and dangers of the drug are acceptable to none more than ourselves, but your leading article does not appear to be a fair assessment of, nor fair comment on, the published work.—We are, etc.,

J. W. MACFARLANE.
J. P. CURRIE.
R. A. PEEBLES BROWN.

Glasgow, C.4.

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1 *Proc. II Cong. Europeo de Rheumat.*, 1951, 417.
2 *J. Amer. med. Ass.*, 1952, **149**, 729.
3 Ibid., 1952, **150**, 1087.
4 Ibid., 1952, **150**, 1084.
5 Cited by Domenjoz, R., *Int. Rec. Med.*, 1952, **165**, 467.
6 Personal communications.
7 *Lancet*, 1952, **2**, 43.

SIR,—That the present enthusiasm for "butazolidin" therapy in rheumatoid arthritis should be tempered is suggested by your leading article (December 27, 1952, p. 1401). We are particularly interested in the medico-legal report in the same issue (p. 1427), in which a case of gastric haemorrhage due to multiple superficial gastric ulcers is reported fully. It may be significant that within the past few weeks two cases have been admitted to the wards with the presenting feature of alimentary tract haemorrhage. Both were females with well-established rheumatoid arthritis and neither gave any former history indicative of disease of the alimentary tract.

The first patient, aged 65, complained of diffuse abdominal pain and of intermittent vomiting of yellow fluid during the seven days preceding the admission. On admission melaena was marked and her haemoglobin was 29% (4.4 g.). She rapidly responded to blood transfusion and iron therapy, and subsequent *x*-ray examinations of the stomach and duodenum were negative. She had been on a dosage of 1 tablet twice daily of butazolidin for three weeks. The second patient was aged 53 and had been receiving 5 tablets of butazolidin daily during the seven days prior to admission. She stated that she had vomited "more than a pint" of fresh blood. Her haemoglobin on admission was 48% (7.1 g.). She responded to iron therapy, but as yet no radiological studies have been carried out.

It will be interesting to observe whether others have witnessed similar episodes of haemorrhage following butazolidin therapy in the absence of former gastro-intestinal disease, and also whether butazolidin might precipitate haemorrhage in those affected with such conditions as peptic ulcer.—We are, etc.,

A. ROSS.
D. W. BALDWIN.

Burnley.

SIR,—Two cases of jaundice following oral administration of "butazolidin" have recently occurred in my practice out of only half a dozen who have so far received the drug.

The first patient, a woman aged 56, was given 1,200 mg. daily, a dosage now regarded as unnecessarily large. On the fifth day she had a severe attack of upper abdominal pain which lasted all night. Two days later she developed jaundice, which cleared within a week. Routine blood tests indicated an obstructive type of jaundice. It was thought at first that she probably had a stone blocking the common duct, but subsequent cholecystography showed a normal gallbladder and no evidence of calculi. It is possible that she had a stone which passed on into the intestine; this cannot now be proved. It was only the occurrence of a second case which led me seriously to consider butazolidin as a cause of her jaundice. The second patient, a woman aged 59, took 600 mg. of butazolidin daily for 24 days, when she stopped it because she had a cold. Two days later she complained of nausea and anorexia, but no pain, and after a further two days became jaundiced. Blood tests again showed a probable obstructive type of jaundice. Now after 10 days her jaundice is fading and her appetite returning.

Jaundice is not mentioned in your leading article on butazolidin (December 27, 1952, p. 1401). Dr. W. A. Bourne mentions three cases in a more recent letter (*Lancet*, January 3, p. 47). Inquiries from friends lead me to believe that it may, in fact, be fairly common. In isolated cases it is almost impossible to establish with certainty that there is a causative relationship between the administration of the drug and the development of jaundice. In the two cases described there is a probability, but no certainty, that butazolidin precipitated jaundice. The matter is, however, important because of the present great popularity of the drug, and further information about it will most readily be obtained if cases of jaundice occurring during the administration of butazolidin are reported, even if, as in those I describe, the causative relationship is not certainly proved.—I am, etc.,

R. M. SOLOMON.

Beaconsfield, Bucks.

Cortisone and Tuberculosis of the Lung

SIR,—Having read with interest various articles on tuberculosis of the lung as a contraindication to cortisone therapy in arthritis, etc., I wondered if cortisone could not be utilized in the treatment of fibrosed nodules in tuberculosis of the lung.

Theoretically, it would seem that, by getting a blood level of streptomycin or isonicotinic acid hydrazide and following by injection of cortisone (after a suitable blood level with streptomycin had been attained), the cortisone would break down the fibrotic tissue in the lung, thus allowing the streptomycin or isonicotinic acid hydrazide to act on the freed tubercle bacilli.—I am, etc.,

D. CHALMERS.

Aberdeen.

Cortisone in Sjögren's Disease

SIR,—In reply to Dr. S. Wiener (December 20, 1952, p. 1357), the case of Sjögren's disease described by me (August 23, 1952, p. 446) has been under the care of ophthalmic surgeons since 1940. At first an application of saline and other simple drops gave little, if any, relief, but some improvement was obtained with artificial tears until the onset of the chest trouble, when there was a setback in the eye condition. The cortisone drops were then given with satisfactory effect.—I am, etc.,

L. B. BOURNE.

London, N.5.

*Grade = Standard measurement of effect of therapy on rheumatoid activity recommended by American Rheumatism Association. Grade I = Complete remission. Grade IV = Complete lack of effect.

Self-demand Feeding

SIR,—I should like to make a few remarks on Professor R. S. Illingworth's interesting letter (December 20, 1952, p. 1355). Self-demand feeding will not fulfil its purpose if it is to become a rigidly imposed doctrine as has been scheduled feeding in the past. Of the many maladjusted children to-day who have failed to fit into their environment a high proportion have broken down under the strain of too great pressure to conform at an age when their capacities for such adjustment were inadequate; but it should not be overlooked that many children have grown up and adjusted themselves in such a regime. I have met mothers who felt so insecure without this kind of order in their lives that the anxiety and tensions which were aroused adversely affected their relation to the baby, and feeding suffered accordingly.

When deciding which method is best the question to be asked is which will suit this particular mother and baby. This can only be decided by the couple themselves. If a free hand is given at the start they will establish a regime that suits them. Feeding is the first social activity the child experiences, and the first social relationship begins then; this lays the foundation for future relationships in the wider social sphere.

An important aspect of wise mothering is the use of a kindly discipline that protects the infant while he is too young to know what is necessary for his survival; but because his needs often cut across his wishes such "discipline" is only possible with a minimum degree of disturbance from someone who has made it her business to understand him and can use it with insight. It would be disastrous, in my opinion, if self-demand feeding should be thought to imply that the mother is to be completely at the mercy of her baby's omnipotent demands, just as it has been disastrous in the past when the baby has been completely at the mercy of such demands from the mother. For this reason I share Professor Illingworth's misgivings about the term "self-demand schedule." It would seem to me only common sense to allow two people who are so important to each other to determine for themselves how best they can establish a good feeding relation.—I am, etc.,

London, W.1. MARION MACKENZIE.

Overfeeding in Early Infancy

SIR,—I was most interested to read "Overfeeding in Early Infancy," by Dr. Ian G. Wickes (November 29, 1952, p. 1178). I found this article very instructive, and there is so much in it with which I agree. I have had over 20 years' concentrated experience in the feeding of infants, and have a vast correspondence with mothers and nurses on this subject.

It is true in most breast-feeding cases that if the infant is allowed to determine his own requirements overfeeding takes care of itself. I have, however, met many cases of definite overfeeding with the symptoms of this disorder as described by Dr. Wickes. Often opportunity for diagnosis is not possible until symptoms and conditions have generally altered and the breast milk is likely to have lessened considerably. Underfeeding may very easily follow overfeeding, and, for this reason, underfeeding is sometimes mistakenly pronounced to be the cause of the original trouble. Diagnosis of overfeeding by reason of a large weight gain alone is not justifiable; other points should also be noted before such a diagnosis can be considered. Babies are individuals, no hard and fast rule can be made, and each infant's particular needs should be respected.

Surely it is misleading to group the breast- and bottle-fed babies together in this discussion? The breast-fed infant can be over- or underfed, but normally the balance of his food remains stable and perfect. In contrast, the artificial mixtures can be variable and the balance should be considered even before quantity per feed. It is pointless to pronounce that the artificially fed infant is either over- or underfed without first knowing the content of his feeds and the proportion of one ingredient to another, as well, of course, as his symptoms. It is, in fact, difficult to overfeed a bottle baby but easy to underfeed him. Refusal to finish feeds often means that his mixture is too concentrated, and I find that appetite sharpens when the balance of the mixture is corrected.—I am, etc.,

The *Nursery World*, London, E.C.4. E. MORRISON.

Parenteral B_{12} in Acute Leukaemia

SIR,—Dr. Ian Welsh (November 22, p. 1133) details his experience with larger-than-ordinary parenteral doses of B_{12} ("ordinary" in this case referring to the dose employed in Addisonian megaloblastic arrest anaemia, to date the only unequivocal indication for B_{12} administration) in acute leukaemia. Results relating to duration of life are tabulated along with a qualitative designation (plus or minus) whether some degree of remission may have been induced. Dr. Welsh seems inclined to the opinion that his results were essentially negative, a conclusion that may also have been implemented by the fact that transfusion and antibiotic administrations were interspersed at the direction of attending physicians, and by Dr. Welsh's apparent cognizance of the additional fact that either of these modalities can be responsible for remission of acute leukaemia.

Whether the B_{12} administered took the form of liver- or streptomyces-derived material and, if the latter, whether it was of "crystalline" or "crude parenteral" grade might be germane to a negative report were it not for the fact that my own experience with any of these sources of B_{12} affirms the modest conclusion reached by Dr. Welsh. My reason for the present affirmation is twofold. First, in 1950, along with Dr. Harry L. Fox, I published a paper entitled "Innocuity of Protracted Administration of Special Fermentation Concentrates of B_{12} as Demonstrated in a Patient with Acute Leukaemia" (*Ohio St. med. J.*, 1950, **46**, 784). The patient remained in prolonged remission, and, though the body of the mistitled paper contains the belated explanation that it was the mycin antibiotic content of the streptomyces-derived fermentation material—not its B_{12}—that induced and maintained remission, we have been erroneously confronted with the advocacy of B_{12} administration for this condition.

That onus might stoically be borne were it not for the second point, that I believe parenteral B_{12} to be not only ineffective but to have been materially harmful to patients whose anaemia is of the erythroblastic arrest (rather than megaloblastic arrest) type, a situation not infrequently extant in the so-called "haemolytic" anaemias as well as the usually refractive anaemia of acute leukaemic subjects. Like Dr. Welsh's conclusion about ineffectiveness, my own on its invidiousness must necessarily rest on impression, but my conclusion in this regard is so strong that I will risk neither its dispelling nor its fortification at the cost of direct human experimentation. The risk would involve the latter, for, on my own acute leukaemic service, needling, whether for supernumerary haematological "follow-up" or for other than urgent medications (and this includes transfusion), is kept at a bare minimum. Opportunity for direct observation has, however, not been altogether lacking, because on other haematological services strong appeal has resided in giving what general physicians have been told is the most active "haematinic" yet uncovered—one that is effective in far smaller amounts than any other common pharmaceutical and, without too much specification around the last point, is completely devoid of toxicity. I have thus seen doses of from 0.1 to 1.0 mg. given to acute leukaemic patients as well as those with aplastic anaemia, not always as a desperation measure, and, though I cannot at present prove my point, I believe the majority of these patients have reacted poorly and have even initiated haemorrhagic phases more than coincidentally to the B_{12} injection. Being without ability to firmly document this belief, refuge must be taken in the rationalization that most acute leukaemic patients are hypersensitive individuals; they react poorly to a host of agents which those who do not have a disease of adaptation will readily tolerate.

The overall life duration in the series presented by Dr. Welsh does not compare unfavourably with numerically equal series in which B_{12} was not given, and this may serve to mitigate a possible contention that such administration is noxious. In fact, these durations are easily as good as, if not better than, in some contemporary series accrued while the aminopterin fiasco was emerging. The justifiability of utilizing life duration figures in comparison has been questioned; their only possible merit lies in overtness, whereas "remission rate" as a therapeutic criterion is open to the more dubious question of definition. Be that as it may, my own life durations of acute leukaemias in a series incorporating all age brackets seem to be significantly greater—whether

statistically significantly so, time alone will tell. In the latter series the mainstay of treatment has been the relentless, continuous daily administration of just enough oral terramycin with milk to maintain a Gram-positive, odourless stool. The severe potassium loss and sodium retention exhibited by many leukaemics on this antibiotic ingestion regime is anticipated and met with a high potassium intake and sodium restriction. Where preponderant mineralocorticoid effects (joint or bone pains, rapidly enlarging glands and intractable oedema) persist, the antibiotic dose is supplemented by a small one of the glucocorticoid, oral cortisone.

The patient's haematomorphology is studiously ignored, because the clinical condition seems a much better index of progress. The numbers of circulating formed elements are permitted to find their own equilibrium level compatible with life, which they frequently do. As a corollary of this fact, transfusions are seldom resorted to; in cases which go on to erythroplasia there is no other alternative than transfusion, but these always take the form of packed, unwashed cells. By studious deletion of those agents which contribute to overtreatment, including B_{12} injections, average life duration in the present series is now about four times that calculated from Dr. Welsh's table. I am hopeful of doing even better in the future.—I am, etc.,

New York City. ROBERT D. BARNARD.

Measurement of Tissue Components Radiologically

SIR,—Dr. Frank Falkner and Miss Sylvia Wisdom in their article "Measurement of Tissue Components Radiologically" (December 6, 1952, p. 1240) appear to have exaggerated the simplicity and accuracy of their "new" technique and also exaggerated the difficulty of the teleradiographic method. With teleradiography the object is not to reduce the overall magnification (which in any case is easily corrected mathematically) but to produce a nearly parallel beam which prevents differential magnification of the tissues being measured due to these lying in more than one plane.

Their technique seems to be based on the false assumption that the outlines of skin, muscle, and bone in a cross-section of a limb may be represented by three concentric circles and that the maximum diameter of all three structures will fall in one plane which will be parallel to the film. In fact, the outlines are neither circular nor concentric, nor are they symmetrical; thus the two points on an outline where the rays of the anode are tangential will often be different distances from the film, thus to measure the diameter of these outlines in one limb by the "new" method six object/film distances have to be measured. Even assuming this can be done, what distances is it proposed to measure—the actual distance between the two points where the rays are tangential or the distance apart in the plane parallel to the film? In either case three exercises in trigonometry will be necessary for each limb.

But can the object/film distances be measured? The shift technique is a well-known method of estimating the depth of opaque foreign bodies. But foreign bodies have fixed identifiable points the shift of which can be measured. With solid objects without recognizable points any tube shift which will produce a measurable shift of the shadow will produce a different profile of the outline so that the tangential rays will cut the outline at different points on this circumference, and it is not difficult to conceive possible limb shapes where these points would be widely separated. The excessively short anode film distance used in the "new" technique will mean that the points on the outline (even a circular outline) where the rays are tangential will not be on the maximum diameter. The error will be greater the larger the diameter and, therefore, disproportionate for the three structures in one limb at a given time and disproportionate between the same structures as the limb grows. The empirical evidence of the two experiments is unacceptable. The experiment with a rigid metal object (we are not told its shape but it, presumably, had fixed points) seems merely a repetition of foreign body localization. The second experiment used only one cross-section of a cadaver. What we need to know is the error involved over the whole range of size and shape of limb cross-sections from infants to adults.

The disadvantages of teleradiography are not as great as Dr. Falkner and Miss Wisdom suggest. The output of the apparatus they employ at 60 cm. is 15 mA for ½ second. Using a distance of 180 cm. (6 ft.) only nine times this exposure is required—namely, 15 mA for one second, or 135 mA for ½ second are appropriate. This compares with their statement that 200 to 400 mA for ½ second is required. Their third criticism of teleradiography is that the centre of the limb can only be guessed and cannot be accurately positioned relative to the film. Substituting a doubtful radiographic technique introduces much more error—for example the image shift measurement, a few millimetres at the most, cannot be judged with any great accuracy bearing in mind that ±½ cm. may represent a 10–20% error. Contrary to the statement of Dr. Falkner and Miss Wisdom, scatter is not influenced by the choice of methods. In the teleradiographic method the beam is limited to the part being examined by devices known as cones. Further, if the examinations are to be repeated often enough for irradiation dangers to be considered then the very short anode film distance of the "new" method will materially increase the dose to the skin nearest to the tube.

Dr. Falkner and Miss Wisdom complain of the expense of apparatus for teleradiography. We doubt if the price of two 15 mA units will be much less than one 100 mA unit, since 15 mA units are in demand for portable work, whereas 100 mA units are obsolete and large numbers have been scrapped recently and are, presumably, available second-hand. The only advantage of the new method over teleradiography, using a 60–100 mA unit, is an insignificant reduction in exposure time which cannot justify the introduction of a "new" technique which appears to have so many sources of error.—We are, etc.,

B. C. H. WARD.
London, S.E.3. G. N. WEBER.

External Popliteal Palsy

SIR,—External popliteal palsy is not quite so simple as Drs. Hugh Garland and Doreen Moorhouse (December 27, 1952, p. 1373) would make it appear. To mention only one difficulty, the bifurcation of the sciatic nerve often occurs inside the pelvis, and then an "uncomplicated" palsy may result from a lesion well above the level of the head of the fibula—for example, in the piriformis muscle, which is frequently pierced by the external popliteal division.

In an article on electromyography (*Lancet*, 1950, **1**, 937), I described a case which resembled several of theirs in that the palsy came on after squatting in an awkward position. But in my case the electromyograph revealed signs of denervation in the short head of the biceps femoris, proving that the lesion was situated at least above mid-thigh level. Weakness of the short head is not easy to demonstrate clinically, because the long head (innervated by the medial popliteal nerve) remains intact; but either head alone can readily be explored with a needle electrode. It is possible that, if the patients of Drs. Garland and Moorhouse had been tested in this way, evidence of lesions above knee level might have been found in some of them.—I am, etc.

London, W.1. FRANK SARGENT.

Smoking and Cancer of the Lung

SIR,—The conclusions of Dr. R. Doll and Professor A. Bradford Hill (December 13, p. 1271) leave no doubt that cigarettes are the main carcinogenic factor in this disease. This is of vital importance to the whole nation. 13,233 people died of this cancer in 1951. A correlation between the rising curve of tobacco consumption with that of deaths from lung cancer, over the last 25 years, suggests that the annual increase of approximately 1,000 deaths will continue until 1965 unless action is taken quickly. It is probable that nearly 25,000 people will die each year by that time. This is a most serious challenge in the social history of our generation. The facts must be made known to the whole community, and the Government, the manufacturers, the medical profession, and the consuming public must face their responsibilities.

The Government problem is primarily one of public health, for many men are dying an avoidable death before the age of 65. Publicity and consequent prevention can only come from central action, and all the power of the Press must be harnessed in this great campaign. A drop in revenue from the tobacco tax is inevitable, but £610m.

annual tax cannot justify silence on the cause of the mounting death rate. The legal responsibility of cigarette manufacturers should be clarified, for it can be an offence to produce goods which are harmful to the health of the consumers. The profession itself must now meet a very personal responsibility in preventive medicine. For years clinicians have tended to pay lip service to the wider aspects of prevention of disease. If we continue to smoke, our patients will follow our example. Are we justified in encouraging them to take this risk? Whatever decision we make about our own health we must tell them of their risk. Doctors who see men slowly dying of this unpleasant and painful death must feel impelled to prevent such deaths in the future. The general public will respond if they are given a sufficiently bold lead. The nation cannot afford to lose many of its most able and industrious men at the peak of their careers.

The following facts should make us press for a saner import policy. Expenditure on the import of cortisone and A.C.T.H. was officially limited to £216,428 in the 12 months ending October 31, 1952. In the 12 months ending March 31, 1951, 221,200,000 lb. of imported tobacco were smoked. Thus beds are filled with dying patients while beneficial and life-saving treatment is denied to sufferers from other diseases.—I am, etc.,

London, N.W.10. HORACE JOULES.

Treatment of a Case of Shock

SIR,—We feel that it may be of value to record the following case of volvulus of the small bowel with vascular collapse treated by intravenous infusion of "levophed" (noradrenaline). We are informed by Messrs. Bayer Products Ltd. that the use of intramuscular ephedrine to facilitate withdrawal of noradrenaline has not previously been described.

The patient, a woman aged 65 years, was admitted on May 10, 1952, with a history of acute abdominal pain which had commenced eight hours previously. Her blood pressure on admission was 135/70 mm. A diagnosis of small-bowel obstruction was made, and gastric aspiration and intravenous saline were commenced in preparation for operation. In spite of this her condition deteriorated rapidly and her blood pressure began to fall. A transfusion of whole blood gave no improvement, and intramuscular and intravenous methedrine was also tried without effect. The blood pressure continued to fall until, five hours after admission, she was in severe shock and the pressure was unrecordable. An infusion of normal saline was set up containing 8 mg. of noradrenaline to the 35-oz. (994-ml.) bottle and the drip commenced fairly rapidly. Within 30 seconds the patient sat up in bed and vomited, and her blood pressure was found to be 160/100 mm. The drip was slowed to approximately 30 drops /min. and the pressure stabilized at 120/80 mm. During transport to the operating theatre the drip was inadvertently speeded up and her pressure rose to 260 mm. systolic. During the operation the systolic pressure was maintained without difficulty at 120 mm. At operation the peritoneal cavity was full of blood and a volvulus of the small bowel was found. The involved bowel was gangrenous and more than 7 ft. (2.13 m.) of small intestine was resected.

Post-operatively it was found to be impossible to discontinue or even slow the noradrenaline drip. Every attempt to do so resulted in an immediate fall in the blood pressure. In addition, it was found that increasing amounts of noradrenaline were required to maintain a steady pressure. It was decided to try the effects of intramuscular ephedrine, and gr. ½ (32 mg.) at three-hour intervals was given. As a result it became possible gradually to slow the noradrenaline drip, and after a further 12 hours it was discontinued completely, with the patient's blood pressure remaining steady at 140/85 mm.

In this case we have no doubt that the intramuscular ephedrine was the operative factor in the stabilization of the blood pressure, and without this the patient would not have survived, as the noradrenaline appeared to have been gradually losing its efficacy over the preceding 24 hours. The patient's subsequent recovery was uneventful, and when last seen she was well and without symptoms.—We are, etc.,

J. WILSON MUGGOCH.
London, E.3. J. R. DYER.

Operative Treatment of Hallux Valgus and Rigidus

SIR,—Mr. N. Ross Smith in his article "Hallux Valgus and Rigidus Treated by Arthrodesis of the Metatarso-Phalangeal Joint," published in your issue of December 27, 1952, p. 1385, claims that the operation he describes will preserve the function of the great toe. He pours scorn on the operations designed to produce a pseudarthrosis of the first metatarso-phalangeal joint because they all fail to preserve this function. The new arthrodesis requires a relatively extensive operation, including fixation of the cartilage-denuded metatarso-phalangeal joint with a screw, stainless steel wire, or staples (either of the two latter admittedly to cause trouble in removal later). After two weeks the foot has to be immobilized in plaster-of-Paris, which has to be retained for six weeks. The metal internal sutures will then need to be removed, and finally adjusted footwear will be required. The advantages claimed over the other operations are that walking in the plaster cast can be started after two weeks and physiotherapy is hardly needed. As a result of all these complicated manœuvres it is stated that there is freedom from pain and disablement in 58% of patients and a further 31% are to be thought satisfactory if sufficient account is taken of the other causes of disablement in the foot.

In the conventional pseudarthrosis operations it is to be expected that, after a fortnight's freedom from weight-bearing and with due attention to the rehabilitation of the intrinsic muscles of the feet, a fully mobile foot will result and that the patient will be capable of walking in normal footwear. Cleveland and Winant[1] published a series of results of 193 Keller's operations for hallux valgus and rigidus, and 93% of excellent results are claimed. Bonney and Macnab[2] published a similar series of 188 arthroplasties and modestly claim reasonably good results, but admit the need for further research.

It is difficult to see why fusion of the first metatarso-phalangeal joint of the foot should be more rational than arthroplasty, or that it can preserve the function of the hallux any better. The author suggests that the failures in his series are caused by fixation of the fused joint at less than 30 degrees of dorsiflexion, but a big toe at such an angle must prove in itself something of a disability when putting on a shoe. Whatever may be gained cosmetically by the new operation is probably lost in the inevitable rigidity of the foot which will result partly from the fused joint and partly from prolonged immobilization of the foot.

Statistically the new operation has no advantages to claim over the conventional arthroplasties, while they have the distinct recommendation that there is a fair chance of restoring the proper muscular control of the foot. The Mayo, Keller, and Girdlestone operations may very well be far from ideal, but at least no farther than the new procedure advocated. If it be conceded that the arthrodesis may finally produce a relatively painless semi-rigid foot which is cosmetically satisfactory, then it might be fairly suggested that a rigid foot equally immaculate cosmetically and quite painless could be more expeditiously produced by amputation below the knee.—I am, etc.,

Leeds. JOHN M. P. CLARK.

REFERENCES
[1] *J. Bone Jt Surg.*, 1950, 32A, 163.
[2] Ibid., 1952, 34B, 366.

Routine Dental Treatment

SIR,—The letter on the above subject from Brigadier R. A. Broderick (January 3, p. 43) is so one-sided as to be misleading. The dental hygienists whom he praises could in their second year be trained to do other operations equally efficiently, and as there are long waiting-lists in every large hospital for children requiring the operation of "Ts. and As." is this his answer?

What of the profession of dental surgery? It became a "closed" profession after much effort in 1921 (long after the medical profession). Are we now to admit "half-

qualified" dentists, and, if so, how is the general public to differentiate? Brigadier Broderick owes it to his juniors that they enjoy the same professional standing as he has done during his professional life. It should be known that it is necessary to acquire the same technical skill to fill both temporary and permanent teeth, and the extraction of temporary teeth is by no means always easy.

The dental schools are full of students training (four years or more) to be fully qualified dental surgeons: are they to be displaced to make room for these "dental nurses"? The idea of utilizing dental nurses emanated from New Zealand, where the conditions for their employment are peculiarly suitable, but these conditions do not exist in this country.—I am, etc.,

Newtown, N. Wales E. DAVIES-THOMAS.

SIR,—Brigadier R. A. Broderick (January 3, p. 43) has mentioned that the British Dental Association is strongly opposed to ancillary dental workers, but has failed to refute its case in any way. He has assumed, perhaps quite unwarrantably, that the large numbers of children with badly decayed teeth are owing to lack of skilled attention being available. He seems to envisage the use of ancillaries in general hospitals to provide "simple fillings" for those who attend, probably both out-patients and in-patients being included. Brigadier Broderick knows as well as any other dental surgeon that spasmodic provision of fillings is worse than useless, and that follow-up inspections and further fillings are essential if further caries is not to destroy teeth already filled. Without adequate follow-up patients lose faith in fillings, and when a dental surgeon tries to persuade them to save teeth at a later stage they refuse point-blank because they know fillings are "no good."

Brigadier Broderick has not said how he could define a "simple filling," nor has he stated what distinguishes a difficult extraction. Surely he is not suggesting that all deciduous teeth are easy to extract. Does he think dental ancillaries could use hypodermic syringes in the mouth, and avoid fragments of carious teeth from being inhaled under general anaesthesia? It would be interesting to know how Brigadier Broderick would answer the British Dental Association's point that to train ancillaries would not increase total dental man-power because the supply of dental teachers is limited and the effective life of women trained in this kind of post is only 10 years; also what objections he has to the British Dental Association's belief that the most effective way to deal with the problem is to enlarge existing dental schools and to turn out more fully qualified dental surgeons.—I am, etc.,

Birmingham. C. N. JEFFRIES.

POINTS FROM LETTERS

Puerperal Psychiatric Illness

Dr. ELLIS STUNGO (London, W.1) writes: I cannot agree with Dr. R. E. Hemphill's emphatic assertion (December 6, 1952, p. 1232) that pregnancy seems to insulate and protect women from psychological and social stresses and strains of the greatest severity." His comprehensive survey of puerperal psychiatric illness was carried out on women delivered at maternity hospitals the majority of whom were, no doubt, either enthusiastic potential mothers, or, alternatively, multiparae who had accepted their pregnancies as a matter of course. My experience of pregnant women has included many who for some reason were unwilling to have the child, and the psychiatric conditions they exhibited have varied from mild reactive depressions to severe schizoid states. I have seen so many cases of attempted suicide in unwillingly pregnant women that I am convinced of their special vulnerability, and I believe that the incidence of suicide in this category of case is high. I certainly agree that women who are desirous of having children appear to enjoy a particular immunity to physical and psychological ills, and I would suggest that the degree of "insulation" varies directly with enthusiasm for their pregnancies. An additional survey to that of Dr. Hemphill's valuable investigation, which I am sure would prove most rewarding, might be conducted into the incidence of psychiatric illness in unwillingly pregnant women before, during, and subsequent to the puerperium. It would be interesting to ascertain the psychiatric history and destiny of women denied a therapeutic abortion. My experience is that a proportion of them either kill themselves, become chronically ill, enter into unsatisfactory marriages with detrimental repercussions on their mental health, or become prostitutes, alcoholics, or delinquents. While the risk of psychiatric illness must not be too readily invoked or exaggerated by doctors sympathetic to the termination of a pregnancy in a particular case, it must not be too lightly disregarded by those antagonistic to interference with an otherwise normal pregnancy. The welfare of the nation is involved either way, and research is urgently indicated into the incidence of psychiatric illness in (*a*) those women whose pregnancies are interrupted on psychiatric grounds and (*b*) those compelled to carry on.

Second Attack of Chicken-pox

Dr. N. H. H. GOLLEDGE (Horam, Sussex) writes: I have had the impression that genuine second cases of chicken-pox were comparatively rare. I have just encountered an example in which the interval between the two attacks was only six months. Both attacks occurred in time of minor epidemic. On the first occasion there was a moderate typical rash, but in the second attack there was a severe eruption preceded by general constitutional upset and headache for three days. The rash was again absolutely typical in appearance and distribution. I should be interested to know whether any of your correspondents have had a similar experience.

"Et all., etcc."

Dr. R. E. M. COKE-HARVEY (Berkhamsted) writes: Dr. A. J. Jex-Blake (December 6, p. 1259) is baying down the scent of an illusory "space-saving abbreviation for the printer." Whereas "*et al.*" for the singular "and another" is a real abbreviation confirmed by time and use, the plural "and others" ("*et alii*") is more elegant and correct, and takes up no more space than "*et all.*" Moreover, if Dr. Jex-Blake wishes to write the neuter form "and other things" ("*et alia*") does he flee the Scylla of the full form for the same old Charybdis of "*et all.*," thereby causing a possible confusion?

Remedy for Drunkenness

Dr. A. H. BARTLEY (Tumatumari, British Guiana) writes: I wonder if any of your readers have ever used any of the intravenous barbiturates when confronted with a wildly excited, abusive, and sometimes dangerous drunkard. As an orderly medical officer in a British colonial hospital in 1948, I was frequently called to deal with such types. They were somehow more quarrelsome, noisy, and dangerous than those met with in the United Kingdom. This of course may be due to the cheap and poor quality liquor consumed. Since all forms of remonstrance and sedation failed to quieten these cases, it occurred to me that an intravenous barbiturate would be effective. I used pentothal sodium 1 g. in 10 ml. distilled water given slowly, as apnoea may occur if given quickly. Immobilization was easily obtained with the assistance of the usually numerous onlookers. The sudden change from bedlam to peace and quietness is so marked that it makes one feel one has really done mankind a service. . . . No dangers or side-effects have been met with in the dozen or so cases I have dealt with.

Any Answers?

Dr. JOHN C. GILLIES (Selby, Yorks) writes: Whoever has had the good fortune to peruse the leading article entitled "The Patient Tells His Story" (December 6, p. 1246) must have observed with regard to the C.M.I. that it trespasses a trifle on the orthodox magnitude of such systems of interrogation. Scorning what we may designate as the customary O.P. investigation, it positively swells into somal and psychical territories far and away beyond the accepted frontiers. Picture to yourself the harassed G.P., ill-tempered, short of time, his attention perforce attracted by the dazzling phantoms of universal benevolence. All other considerations drop from his mind what time he struggles to grasp the collective interests of the species. No 195 questions for such wretches as he who toil behind the testimonial curtain. Only one question, essential, overriding, and universal, waits for an answer, "Do you want a certificate?"

Correction

It is regretted that the word "Foley" was wrongly inserted in the last sentence of a letter from Mr. B. H. Page on "The Catheter and the Prostate" (see *Journal*, December 27, 1952, p. 1415), and this resulted in restricting the meaning of the sentence. Mr. Page wished to draw attention to a complication caused by various types of rubber catheter and probably least of all by the Foley type.

Obituary

CHARLES H. MELLAND, M.D., F.R.C.P.

Dr. Charles Melland died in Manchester on January 8 at the age of 80. With his passing Manchester has lost not only a distinguished physician but the last member of a family which has given its service in the best medical tradition for well over a century.

Charles Herbert Melland, whose father, Frederick Melland, was a Manchester surgeon, was born on October 20, 1872. From Manchester Grammar School he went on to Owens College. After a distinguished career as a student—he won the Platt Physiology Exhibition—he qualified in 1894, graduated M.B. (London) with first-class honours in 1897, and proceeded M.D. in 1900.

He held a number of senior house appointments, serving as resident medical officer at the Manchester Royal Infirmary and at the City of London Hospital for Diseases of the Chest, Victoria Park. In 1902 he became a Member of the Royal College of Physicians, and two years later he took the B.Sc. of Victoria University. From 1901–5 he was director of the clinical laboratory at the Royal Infirmary. During his years of study he widened his knowledge by Continental travel and increased his medical experience in the clinics of Vienna and Graz. On his return to Manchester he started consulting practice, and became a physician to Ancoats Hospital, to which he gave devoted service until his resignation from it in 1914 on his election to the staff of the Royal Infirmary. From then on until his retirement from the active staff in 1932 he was a teacher and was able to be in contact with a rising generation: the association was a happy one for both teacher and students.

In 1906, when the Royal Commission on the Care and Control of the Feeble-minded was collecting evidence, Melland was appointed medical investigator, and his report on the incidence of feeble-mindedness and epilepsy in Manchester was embodied in the commission's blue book. As a result of this work he was appointed honorary physician to the National Association for the Care of the Feeble-minded. In the 1914–18 war he served in the R.A.M.C., being attached to the Second Western General Hospital. Dr. Melland was elected F.R.C.P. in 1921.

T. H. O. writes: As a physician, trained in the old order before the advent of *x* rays and the clinical laboratory, Charles Melland proved himself a man of vision who kept abreast with the times, and though his particular interests were diseases of the blood his knowledge was wide and his clinical acumen was always regarded with respect. He himself, even in his later years, remained a man of broad outlook, interested in many branches of knowledge. Despite an increasing lameness he was often to be found at medical gatherings, delighting on more convivial occasions to meet his colleagues at some reunion or dinner, and it was obvious how much he enjoyed the gathering of his friends to celebrate his eightieth birthday. Apart from medicine, two things interested him to the very end—mountains and lacrosse. As a young man he had been a noted lacrosse player, and even in old age he would travel long distances in order to watch the fortunes of the university team. Although not a mountaineer in the strict sense of the word, he had an abiding passion for mountains, and whether fell-walking in the Lakes or in Wales, or on holiday in the Dolomites or Alps, he found in them something which stirred his imagination and brought content. His memory was stored with them and he would delight to talk of them, even about those which he had never seen.

Kindly and considerate, Charles Melland upheld a great tradition and we feel the poorer for his loss, and if in later years an increasing infirmity and the loss of a loved wife marred his old age it was borne cheerfully and with courage, and death came mercifully and without pain. He leaves a son and daughter, to whom we offer our sincerest sympathy.

HAROLD ORR, O.B.E., M.D., F.R.C.P.(C.), F.A.C.P.

For the first time in its history the Canadian Medical Association lost its serving President by death when Dr. Harold Orr, of Edmonton, Alberta, died in Toronto on December 26, 1952. Dr. Orr assumed the presidency of the association at its annual meeting in Banff in June last year. During the three succeeding months he and Mrs. Orr travelled more than 8,000 miles in Canada attending the annual meetings of the provincial divisions of the association. Early in October he departed for Athens to represent Canada at the Sixth General Assembly of the World Medical Association. Shortly after his arrival in Greece the first signs of coronary insufficiency presented themselves, but Dr. Orr managed to carry on until his return to London, England, where he was in hospital for three weeks. He then departed for home by boat, but on arrival in New York was again obliged to enter hospital, where he remained for four weeks. Once again he resumed his homeward journey, getting as far as Toronto, where he suffered a very severe coronary occlusion from which he failed to recover.

Born in Toronto in 1889, Harold Orr graduated in 1911 at the University of Toronto. He engaged in general practice in Medicine Hat, Alberta, until the outbreak of the first world war, when he joined the Canadian Army Medical Corps and served as a medical officer for five years, being twice mentioned in dispatches. He returned home with the rank of lieutenant-colonel, and was awarded the O.B.E. After training in dermatology and syphilology in London, Dr. Orr established himself in specialist practice in Edmonton, and was appointed clinical professor of dermatology and syphilology in the faculty of medicine, University of Alberta. For more than 20 years he most efficiently supervised the division of venereal disease control in the department of public health of the Province of Alberta.

While a comparatively young man, Harold Orr had crowded into his life a full measure of accomplishments of which any member of the medical profession could be justly proud. Always interested in the welfare of his chosen profession and the community in which he served, he could be counted upon to assume with cheerfulness whatever responsibilities were laid upon him and to carry them out with efficiency. He had served as president of the Alberta Division prior to his election to the office of President-Elect of the Canadian Medical Association. In debate he was clear, incisive, and always fair. He possessed those rare qualities of head which permitted him to get to the heart and core of a question quickly and intelligently.

Canadian medicine mourns the passing of a great leader, a warm-hearted companion, and a brilliant mind. He made his contribution to humanity in full measure. He leaves to mourn him his wife and one daughter.—T. C. R.

ROYDEN S. WALE, M.D., F.L.S.

Dr. R. S. Wale, who was pathologist to the Leicester General Hospital, died in London on November 21, 1952, at the early age of 45.

Royden Samuel Wale was born on December 22, 1906, and was educated at King's College School, Wimbledon, and at King's College Hospital, where he graduated M.B., B.S. in 1931, and he was a keen and competent athlete, playing rugby football, squash rackets, and tennis for his hospital. His love for pathological work was kindled while he was a dresser to the late Sir G. Lenthal Cheatle, and in 1930 they published jointly a short paper on "A Lesion Common to Breast and Prostate Glands" in the *British Journal of Surgery*. After graduating in 1931, Wale worked under Dr. R. D. Lawrence in the diabetic department and under the late Dr. E. ff. Creed in the pathological department at King's College Hospital, which he left after holding a series of appointments to become assistant pathologist at the Royal Cancer Hospital. He proceeded M.D. in pathology in 1935. At the outbreak of war in 1939 his services were retained in the Emergency Medical Service, and in 1942 he was placed in charge of the pathological department of the Leicester General Hospital, where he quickly endeared himself to his colleagues and associates. His main medical interests were morbid anatomy and histology, but his library of books on physics, astrophysics, mathematics, botany, entomology, music, and the theatre was a hall of mirrors reflecting many facets of his versatile mind. Like so many medical men, he developed an interest in alpine flora. As a result of his own excursions to the Balkans and with the help of friends who travelled abroad he amassed a unique collection of semperviva, which he cultivated and studied, ultimately attempting to clarify and reclassify the genus in articles published in the *Bulletin* of the Alpine Garden Society. His work brought him national and international recognition, and his election as a Fellow of the Linnean Society in 1936 attested to the value of his investigations.

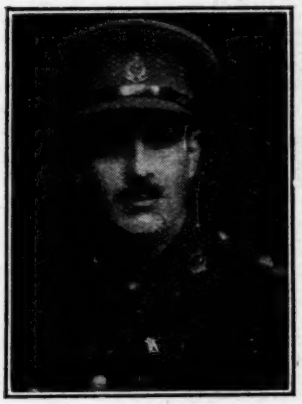
Wale also willingly undertook administrative responsibility and became secretary, and later chairman, of the Leicester General Hospital medical consultants committee. He sought tirelessly to encourage hospital improvements and to wed the best of the old medical service to the good of the new National Health Service.

It was some eight years ago that he first diagnosed his own lymphatic leukaemia. It remained an everlasting source of wonder, admiration, and inspiration to many of us who worked with him to see how calmly and unembittered he bore his cross. His kindness, forbearance, and consideration for both the medical and domestic staffs will long be remembered. When life became a frightful burden his courage and sweet stoicism glowed ever brighter.—J. O.

M. H. WOSTENHOLM, F.R.C.S.

We record with regret the death on December 12, 1952, as the result of a motor accident, of Mr. M. H. Wostenholm, who was an ear, nose, and throat surgeon at the Bedford General Hospital. His wife was killed at the same time.

Born on May 31, 1915, in South Africa, Maurice Humphrey Wostenholm came to England in 1935 to study medicine at Cambridge and at the London Hospital, where he qualified M.R.C.S., L.R.C.P. in 1941. After holding resident appointments at the London he joined the R.A.M.C. in 1942, and served until 1946 as a graded surgeon with the rank of captain. On his return to civil life he was appointed first assistant in the aural department at the London Hospital, and in 1947 he became F.R.C.S. He was appointed a consultant ear, nose, and throat surgeon on the staff of the Bedford General Hospital about 18 months ago, and he also held an appointment at St. Albans City Hospital. Mr. and Mrs. Wostenholm leave three young sons.



Dr. DAVID LEWES writes: The tragic news of the sudden death of Maurice Wostenholm and his wife will fill with sorrow all who were privileged to know that able young surgeon. Those whose good fortune it was to come into contact with him will bear testimony to his spontaneous kindliness, and his patients will always remember him with gratitude both for his skill as a surgeon and for his whole-hearted sharing of their personal problems. From his earliest days at the London he was fired with enthusiasm in all he did, and his gay spirit, which was infectious, livened and cheered his many friends. He worked hard and played hard. In his daily life he gave vital meaning to the motto above the entrance to the medical college where he worked: *Amara lento tempera risu*—temper the difficult things in life with a smile. He faced difficulties with a slow smile and he possessed in rich measure those rare qualities—equanimity and imperturbability. Our hearts go out in sorrow to his parents and to other relations and to his three little boys.

Mr. KENNETH B. BELLWOOD writes: In the tragic death of Mr. Maurice Wostenholm, Bedford General Hospital has lost a most vital and capable member of the staff; indeed, in the 18 months, or even less, since he joined us he had already become much liked and respected. In the ear, nose, and throat department, in which we were jointly responsible, I soon became aware of his amiable and helpful character. Both as a clinician and as a surgeon he had good experience and judgment. It was always pleasant to meet and to discuss matters with him, and I regret that our friendship was so soon cut short, when it seemed that he was keen to develop the department both now and in the future. We have lost a young and a most promising friend and colleague.

Dr. M. D. C. HOSFORD writes: Mr. Wostenholm's work as a surgeon was brilliant, and his enthusiasm, energy, and tireless attention to all the details of his work will make his tragic death at the outset of a brilliant career a serious misfortune to his patients and all with whom he worked. He and his wife were delightful companions and will be missed by a wide circle of friends.

Dr. LESLIE EDWARD HUGHES, who died on January 4 at the age of 75 after a short illness, was born on May 15, 1877, the youngest son of the late Dr. D. W. Hughes, of Wymond-

ham, Norfolk. He was a medical student at St. Bartholomew's Hospital, and after qualifying in 1902 he put in the long period of six years in various house appointments at the Norfolk and Norwich Hospital, finally becoming senior resident surgical officer there. Throughout his life he was very keen on surgery and midwifery, and when he joined the late Dr. C. P. Hooker in partnership at Cirencester in 1907 he quickly made a name for himself as a sound surgeon and an exceptionally good accoucheur. Indeed, his figure of 3,000 confinements with only two maternal deaths—confinements often carried out in home conditions leaving much to be desired and without all the modern advantages and with no institution for difficult cases—is one which cannot often have been surpassed. As a surgeon to Cirencester Memorial Hospital he proved his skill and judgment over many years. At the outbreak of war in 1914 Dr. Hughes offered his services to the R.A.M.C., but his offer was refused, as he was just over the age limit prevailing then. Not to be deterred from serving his country, Dr. Hughes enlisted in the Grenadier Guards and went through the recruits' training for three months. Representations from influential quarters secured a relaxation of the age limit in his case, and he was posted as medical officer to the Gloucester Regiment. He went on active service in 1915 as regimental medical officer to the Oxford and Bucks Light Infantry, and remained with the unit until the autumn of 1918, when he was promoted temporary major and posted as surgical specialist to a casualty clearing station on the Murmansk front. He was mentioned in dispatches four times, was awarded the Military Cross, and was recommended for the D.S.O. Returning to Cirencester in 1919, he resumed his partnership until Dr. Hooker's retirement, and he then continued in single-handed practice until his own retirement in July, 1948. He had great misgivings about the new National Health Service Act. Dr. Hughes was a keen shot and took a great interest in the work of the British Legion, having been chairman of the benevolent committee of the Cirencester branch for many years. He was unmarried.—J. H. G.-W.

Medico-Legal

DAMAGES AGAINST CASUALTY OFFICER

In the recent case of *Payne* v. *St. Helier Group Hospital Management Committee and Another*, the court held that a casualty officer at the hospital had been negligent. Since the casualty officer was employed by the management committee of the hospital, the hospital also became liable, but, in awarding damages to the plaintiff, the judge made an order indemnifying the committee against the doctor in respect of the whole sum awarded as damages, and in respect of two-thirds of the committee's costs. Because of some notable features the case is reported at length below.

The plaintiff, Mrs. Payne, was the widow of a horsekeeper employed by United Dairies. At about 5 o'clock in the morning of July 10, 1950, Mr. Payne was kicked in the abdomen by a horse that slipped when he roused it. He consulted his doctor, who referred him to the hospital. A casualty officer examined him at 2.30 p.m., some 9½ hours after the injury had been sustained. This practitioner had been professionally qualified for two years. He observed and recorded in the notes a bruise as large as the palm of a hand in the right iliac fossa. He recorded also that there was no sign of bony or visceral injury. He sent the patient home to go to bed and to call in his own doctor.

On July 28, eighteen days later, the patient had become very ill, and was readmitted to hospital. The diagnosis made on admission to hospital was extra-peritoneal haematoma. An operation was performed on August 2. No extra-peritoneal haematoma was found, but the peritoneum was punctured with the finger of the operator and gas and faecal pus escaped. The wound was drained. A further operation was performed on August 21 for general peritonitis and faecal fistula. The patient's condition was by this time very poor, and an anastomosis was made of small bowel to transverse colon. Death followed on August 30, 51 days after the original accident.

Mrs. Payne, the widow of the deceased, said in evidence that her husband had vomited after his arrival home from work on the morning of the injury. He had also vomited repeatedly while at home after return from hospital. He was able to keep nothing down, not even a switched egg. During the period when he was at home he got up for necessary purposes, came down for short periods to sit by the fire, and went out a little. On one occasion he had attended for a short time a cricket match in a neighbouring sports field.

Casualty Officer's Evidence

The casualty officer in evidence stated that, when he first examined the deceased on his arrival at hospital on the day of the injury, he had found slight surface bruising of the right iliac fossa. He had palpated the abdomen, and the bone, but had been unable to find any sign of bony or visceral injury. The abdomen was soft and moved with respiration, it was not tender, there was no muscle guarding, and sounds of bowel movement could be heard. There was nothing abnormal in the man's pulse rate and he was not in any way collapsed. He had told the patient to go home and go to bed and to call in his own doctor.

General Practitioners' Evidence

The patient's general practitioner said in evidence that when he had sent the patient to hospital he had had in his mind that the surgical consultant would be in attendance at the hospital on that afternoon and would have an opportunity of seeing him. He wished in the case of such an injury to have a second opinion. He did not specifically ask in his letter of recommendation for a consultant's opinion. On the following morning Mrs. Payne had called at his surgery and told him that there was no internal injury, and that the injury was not considered to be serious, but that she had been asked to call her own doctor in again. He saw the patient next morning and examined him. There was still some tenderness but rather less than on the previous day. Shock was less marked and he seemed to be a little better. There was definitely no deterioration in his condition on this occasion. He told him to rest and to let him know if anything went amiss. He got no further call to see Mr. Payne, but visited him on July 17, when he was still in bed. He was getting up to go to the toilet and had had some diarrhoea. There was no other abdominal symptom and the bruising was less. He did not remember Mrs. Payne or her husband mentioning vomiting to him; had either done so he would certainly have referred the patient to hospital again. He told Mr. Payne that he was going on holiday on July 18, but that he should see on July 24 the colleague who was doing his holiday work, and who would come and visit him before if he felt worried in any way.

Mr. Payne did in fact visit this colleague on that date and informed the colleague, it was said in evidence, that he was feeling much better and anxious to return to work, but was still troubled by a fair amount of wind. This doctor said in evidence also that the patient appeared strained, but that his abdomen presented no tenderness whatever and no muscle guarding. There was a suggestion, however, of some abdominal distension. He did not remember Mrs. Payne or her husband mentioning vomiting to him; had either done so he would certainly have referred the patient to hospital.

On July 28 this doctor had a call from Mrs. Payne and visited the patient again in his home. He was in bed in a cold sweat, his breathing was somewhat laboured, he looked drawn, and was a very sick man. His abdomen was grossly distended. With a diagnosis of early paralytic ileus he referred the patient to hospital for admission. He did not at that time present the signs of peritonitis.

On admission to hospital, as recorded above, the two successive operations were performed and the patient died on August 30.

Evidence of the post-mortem findings was given by Dr. David Haler, the coroner's pathologist. He had found at necropsy a state of general peritonitis, a subphrenic abscess, a bruise of the abdominal wall and necrosis of the muscles in the hollow of the ilium, necrosis and perforation of the caecum, an external fistula from the caecum through the wound of the first operation, and the anastomosis which had been performed at the final operation. He gave it as his opinion that the caecum had been bruised at the time of the original injury and that, if operation had been performed then, the subsequent course of the patient's illness and his death would in all probability have been averted.

Expert Witnesses

Sir Hugh Griffiths, surgeon to the Albert Dock and other hospitals, gave it as his opinion that the caecum had been bruised by the original injury, and that an abscess had formed in relation to the bruised caecum, bursting later to give a general peritonitis and to occasion death. He was of opinion that if the patient had been submitted to operation at the time when he was first sent to hospital the later effects of the injury would have been avoided by prompt attention to the bruised caecum. Bruising could not occur from the impact of force unless tissue was bruised between that force and a hard structure such as bone. The bruising of the right iliac fossa indicated that the tissues of the right iliac fossa had been pressed between the horse's hoof and the hollow of the ilium. The caecum would anatomically lie between the force of the hoof and that bone. He took a serious view of all abdominal injuries and had made it a rule in his hospital that all abdominal injuries, like all head injuries, were admitted for 24 hours for observation at least. He did not regard one act of vomiting after such an injury as necessarily serious; but, with that amount of bruising, if a patient had vomited on more than one occasion he would operate, even in the absence of signs of perforation. By so operating, bruised bowel could be removed before actual perforation occurred. He did not blame the casualty officer—it was inexperience.

Professor Ian Aird said in evidence that he was puzzled by the whole circumstances of the case and could not explain why peritonitis had occurred so late. Perforation of the caecum and necrosis of the caecum which was productive of peritonitis could not be present for more than a few days. He suspected that the subphrenic abscess, a condition notoriously difficult to detect, and which was certainly present at death, had played a more important part than had been suggested by other evidence. He would not have operated on the day of the injury in the presence of the symptoms and signs which had been described. He would not operate even in a case of suspected bowel rupture unless there were actual signs of perforation, tenderness, and rigidity of the abdominal muscles at least. He did not regard bruising of the character described, even if associated with vomiting on two occasions, as an indication for abdominal exploration. He did not think necessarily that the patient should have been admitted when he presented at hospital. It was desirable to admit for observation patients after abdominal injury of this kind who were seen within a short time of the injury, but, if there were no signs of perforation present after nine and a half hours, it was safe to conclude that no urgent emergency would be likely to arise and to permit the patient to return home to the care of his own doctor. He did not believe that the severity of an injury could be deduced from the presence or extent of bruising, and he could not agree that for bruising to occur it was necessary for tissues to be compressed between an external force and bone. An external force alone could cause bruising to soft tissues, as it did for instance in the loin quite commonly, where there could be no question of crushing of tissues against the distant spine; such organs as the brain and the lung too could be bruised within the intact walls of the cavities which enclosed them. He thought it wrong to conclude that earlier operation, even if it had been performed in this case, would have averted the later consequences. He found it impossible to say at what time he would have advised that operation be done in this particular case. The patient was not thought to be in urgent need of operation even when finally admitted to hospital 18 days after the original injury.

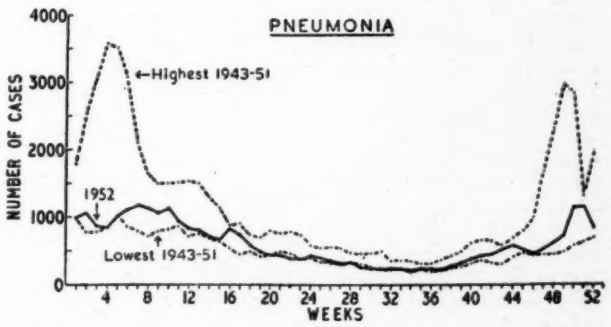
Judge's Comments

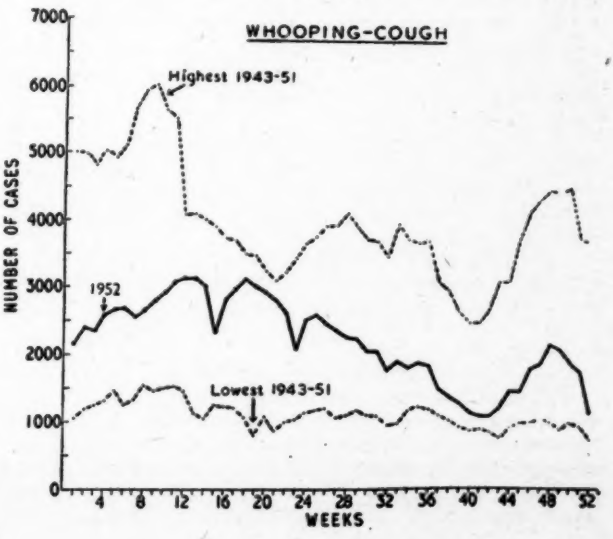
Mr. Justice Donovan awarded the widow £2,640 in damages, holding that the casualty officer was wholly liable and indemnifying the hospital in respect of its responsibility for him. He admitted that the clinical tests made by the casualty officer were correct, but he was of opinion that the casualty officer had failed to observe a rigidity of the abdomen which must have been there, and to notice that the patient was suffering from pain and shock. If these conditions were present in addition to the bruising, then the diagnosis and treatment represented less than the exercise of reasonable care. It was wholly unjustifiable to send the man home and not to detain him for examination by a consultant. It was reasonable to conclude that, if the man had been seen by a consultant, timely operation would have been performed, and the deceased in all probability would have survived.

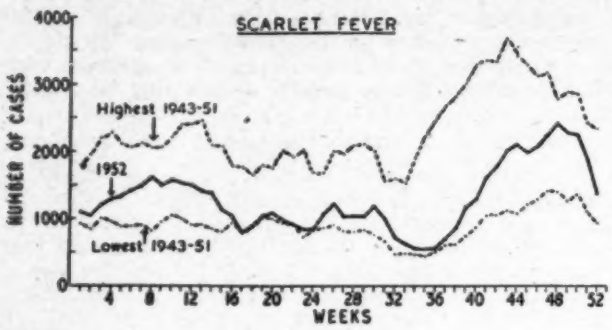
Vital Statistics

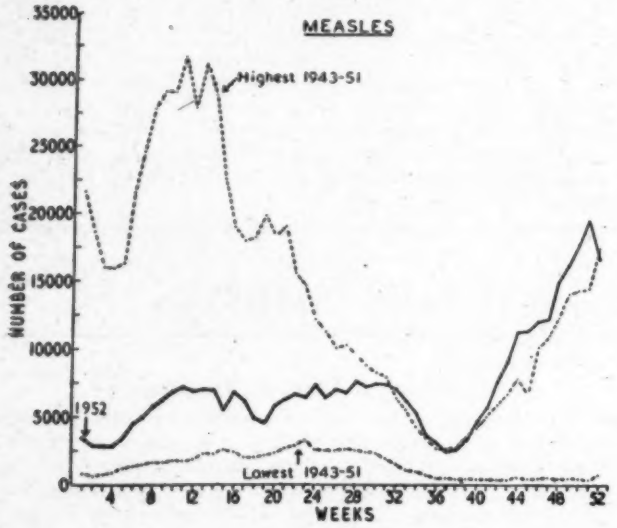
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1943–51 are shown thus - - - - - - -, the figures for 1952 thus ———. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

A large fall occurred in the number of notifications of infectious diseases in England and Wales during the week ending December 27, 1952. The largest decreases in the number of notifications were 5,262 for measles, from 19,551 to 14,189, 631 for whooping-cough, from 1,748 to 1,117, 523 for scarlet fever, from 1,881 to 1,358, and 143 for dysentery, from 327 to 184.

The largest declines in the incidence of measles were 912 in Essex, from 2,327 to 1,415, 801 in London, from 1,797 to 996, 545 in Middlesex, from 1,329 to 784, 410 in Kent, from 1,181 to 771, and 301 in Yorkshire West Riding, from 1,297 to 996. The largest falls in the number of notifications of whooping-cough were Lancashire 69, from 290 to 221, and Cheshire 63, from 134 to 71. The largest decreases in the incidence of scarlet fever were Essex 77, from 162 to 85, and Lancashire 59, from 229 to 170. During the week 26 cases of diphtheria were notified, 3 more than in the preceding week. No case of diphtheria was notified in the southern section of the country comprising London, the south-east, the south-west, and the south midland counties.

33 cases of acute poliomyelitis were notified; these were 5 fewer for paralytic and 9 fewer for non-paralytic cases than in the preceding week. The largest returns were Middlesex 4, Sussex 3, and Berkshire 3 (Maidenhead M.B. 3).

The largest centres of dysentery were Lancashire 44 (Liverpool C.B. 21), Lincolnshire 38 (Grimsby C.B. 37), London 23, Kent 23 (Penge U.D. 19), and Westmorland 13 (Kendal M.B. 13).

Week Ending January 3

The notifications of infectious diseases in England and Wales during the week included scarlet fever 1,716, whooping-cough 2,165, diphtheria 25, measles 30,497, acute poliomyelitis 37, dysentery 262, paratyphoid fever 0, and typhoid fever 1. The number of measles notifications is about double that of the previous week.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending December 27 (No. 52) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	26	0	10	1		43	3	13	0	2
Dysentery	184	23	75	2	1	293	17	84	0	
Encephalitis, acute	6	0	0	0		0	0	0	0	
Enteric fever: Typhoid	2	0	0	0		3	2	1	0	0
Paratyphoid	3	0	0	0		7	0	1(B)	1	
Food-poisoning	42	0		1		449	7		0	
Infective enteritis or diarrhoea under 2 years				8	1				14	9
Measles*	14,189	996	103	17	40	2,331	19	84	106	42
Meningococcal infection	31	3	14	2		26	4	15	1	1
Ophthalmia neonatorum	9	1	10	0		20	0	9	0	
Pneumonia†	826	44	284	1	2	678	30	245	4	
Poliomyelitis, acute: Paralytic	30	2	2	0		17	2	3	0	
Non-paralytic	3	0				3	0			
Puerperal fever§	145	17	13	1		131	21	13	1	
Scarlet fever	1,358	72	264	14	52	1,095	72	281	12	41
Tuberculosis: Respiratory			123	21				142	18	
Non-respiratory			23	4				29	8	
Whooping-cough	1,117	73	61	11	12	1,402	73	230	60	22

DEATHS in Great Towns	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	1		0	*1*	0	*1*	0	0
Dysentery	0	0					0		0	
Encephalitis, acute		0			0	*0*	0	*0*	0	
Enteric fever	0	0	0							
Infective enteritis or diarrhoea under 2 years	11	2	3		1	*12*		*3*	0	2
Influenza	44	6	2		1	*22*	5	*0*	0	0
Measles		0	1		0		0	*0*	0	0
Meningococcal infection		2	1				0	*1*		
Pneumonia	449	91			9	*250*	44		7	6
Poliomyelitis, acute	2	0			0	*0*	0			0
Scarlet fever		1	0		0		0	*0*	0	0
Tuberculosis: Respiratory	120	21	27		3	*131*	11	*28*	10	5
Non-respiratory		2	5		0		0	*2*	0	0
Whooping-cough	6	0	0		0	*0*	0	*2*	1	0
Deaths 0–1 year	249	23	29		13	*217*	30	*35*	4	9
Deaths (excluding stillbirths)	6,472	1029	763		173	*5,033*	816	*612*	115	104
LIVE BIRTHS	4,450	623	778		254	*5,082*	707	*804*	138	91
STILLBIRTHS	133	11	30			*159*	25	*34*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Careers in Medical Research.—The Medical Research Council has issued a useful pamphlet entitled "Opportunities for Appointment to the Scientific Staff" for those considering a career in medical research. The pamphlet deals briefly with the Council's constitutional position and states the conditions of work and terms of service for its staff. Then follow a classified survey of the current research programme and a list of the Council's establishments. The Council's method of recruitment is by recommendation from the director of the unit at which an applicant wishes to work. Copies of the pamphlet may be obtained, free on request, from the secretary, Medical Research Council, 38, Old Queen Street, London, S.W.1.

Travelling Medical Fellowships.—The Medical Research Council invites applications for the following Travelling Fellowships for the academic year 1953–4:

Rockefeller Fellowships.—These Fellowships are intended for graduates who have had some training in research work in clinical medicine or surgery, or in some other branch of medical science, and who are likely to profit by a period of work at a centre in the United States or elsewhere abroad, before taking up positions for higher teaching or research in the United Kingdom. Fellowships tenable in the United States will normally carry a maintenance allowance at the rate of $2,600 per annum for a single Fellow and $3,600 per annum for a married Fellow. Provision will also be made for travelling and other approved expenses. The last date for application is March 15.

Eli Lilly Fellowships.—Four Fellowships, tenable in the United States, will be available for the academic year 1953–4, and the awards will in general be made on terms and conditions similar to those attaching to the Rockefeller Travelling Fellowships in Medicine. The last date for application is March 15.

Dorothy Temple Cross Research Fellowships.—The object of these Fellowships is to give special opportunities for study or research to suitably qualified British subjects "intending to devote themselves to the advancement by teaching or research of curative or preventive treatment of tuberculosis in all or any of its forms." The Fellowships will, as a rule, be awarded to candidates who wish to make their studies or inquiries elsewhere than in the United Kingdom. The Fellowships provide for the payment of a maintenance allowance at the rate of £650 per annum for a single Fellow and £900 per annum for a married Fellow, subject to appropriate adjustment in the case of Fellowships tenable at centres outside the sterling area; in addition, an allowance will be made for travelling and other approved expenses. The last date for application is March 15.

Alexander Pigott Wernher Memorial Fellowships.—These Fellowships are intended for suitably qualified medical graduates who are likely to profit by a period of work in ophthalmology or otology at a centre abroad before taking up positions for higher teaching and research. The awards, which will normally be tenable for one year, are at the rate of £650 per annum for a single Fellow or £900 per annum for a married Fellow, subject to appropriate adjustment in the case of Fellowships tenable at centres outside the sterling area. In addition, an allowance is made for travelling and other approved expenses. The last date for application is March 31.

French Government Exchange Scholarships.—Under the terms of a reciprocal arrangement with the Centre National de la Recherche Scientifique two scholarships, tenable at research institutions in France during the academic year 1953–4, are open to British workers in medical science (excluding clinical medicine). The scheme is intended for young graduates in medicine or science who have already had some experience in a branch of medical science. Candidates must be of British nationality and have at least a working knowledge of French. The scholarships will normally carry a maintenance allowance within the range of 45,000–90,000 francs a month, according to qualifications and experience, and married men will receive a supplementary allowance (payable in sterling by the Council). Provision will also be made for travelling expenses to and from the place of work. The last date for application is March 31.

Further details of these Fellowships and forms of application may be obtained from the Secretary, Medical Research Council, 38, Old Queen Street, London, S.W.1.

Anglo-French Exchange Bursaries.—Applications are now invited for bursaries which will be awarded this year to young British doctors under an exchange scheme arranged by the French Embassy in London between the Institut National d'Hygiène, in Paris, and the Ciba Foundation, in London. The value of the French grants is 60,000 francs a month, tax free. Grants will be awarded for periods of two to four months to doctors who wish to obtain clinical experience or carry out medical research in France. Applications for the bursaries should be sent before March 31 to Dr. Wolstenholme, Director, Ciba Foundation, 41, Portland Place, London, W.1.

Scholarship for Medical Women.—The Royal Society of Medicine announces that a William Gibson research scholarship will be awarded in July to date from October, 1953. The scholarship, which is tenable for two years and is at the rate of about £200 a year, is open to "qualified medical women who are subjects of the British Empire." Further details may be obtained from the secretary, Royal Society of Medicine, 1, Wimpole Street, London, W.1. The last date for applications is June 1.

Laboratory for Dr. Funk.—On January 13 Dr. Louis H. Bauer, president of the American Medical Association, presented a new research laboratory to Dr. Casimir Funk, the noted biochemist who coined the word "vitamin" (originally "vitamine"). The laboratory, which is in Manhattan, New York, was paid for by the Funk Foundation for Medical Research, a fairly recently founded non-profit organization interested especially in cancer research. Here Dr. Funk is proposing to carry out a much-expanded research programme. Dr. Funk was born in Warsaw 69 years ago, and it was while he was at the Lister Institute, London, that he did much of his well-known work on the metabolism of the B vitamins.

Care of the Premature Baby.—The Southmead General Hospital Group Management Committee has published a booklet called "The Care of the Premature Baby in the Bristol Area." Prepared jointly by the departments of child health and public health, the booklet describes the services which have been developed at Bristol to deal with premature infants. It was originally intended for private circulation among paediatricians and laymen faced with establishing similar services, but in view of the large demand it is now made more widely available. Copies may be obtained from the Management Committee, Southmead Hospital, Bristol.

Sir Heneage Ogilvie, consulting surgeon, Guy's Hospital, has been appointed praelector in the faculty of medicine at St. Andrews University for the session 1952–3. During his tenure of office he will take part in the teaching and clinical work of the department of surgery and deliver a series of open lectures.

Professor F. H. Bentley has resigned the Chair of Surgery in the University of Durham to take up a research and teaching appointment under the Sommer Memorial Trust, combined with the practice of surgery, in Portland, Oregon.

Star and Garter Home Commandant.—Colonel Geoffrey Anderton has been appointed Commandant of the Star and Garter Home for Disabled Sailors, Soldiers, and Airmen at Richmond in Surrey in succession to Major Cecil Burnham. Colonel Anderton entered the R.A.M.C. in 1928, and in the last war he was mentioned in dispatches in 1943 and in the following year was appointed O.B.E.

Emergency Bed Service: Applications and Admissions.—During the seven days ending January 12 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 1,758, of whom 80.78% were admitted. A white warning, indicating that the percentage of admissions fell to 82½, was issued on January 6.

COMING EVENTS

Health in Industry.—The Industrial Welfare Society has arranged a course of lectures on "Positive Health Measures in Industry." The lectures, all of which begin at 6 p.m., are to be held at the offices of the Society, 48, Bryanston Square, London, W.1. The titles and speakers are as follows: January 22—Organization of First Aid in Work Places, by Dr. Neil G. Marr; January 29—Sickness Absenteeism, by Dr. P. Fitzsimons; February 5—Posture and Movement in Relation to Industrial Health, by Dr. W. F. Floyd; February 12—Health Education in Industry, by Dr. F. M. Oldershaw. The fee for the course is £1 10s. for members and £2 for non-members. Further information may be obtained from Mrs. O. K. Skelley, Industrial Welfare Society (Inc.), 48, Bryanston Square, London, W.1.

Postgraduate Course for General Practitioners.—Cambridge University Medical School has arranged a further postgraduate course at Addenbrooke's Hospital, Cambridge, on January 24 at 10.30 a.m. It will take the form of a symposium on radiotherapy, and will include lecture-discussions and demonstrations. The course is open, free of charge, to general medical practitioners whose names are on the National Health Service list. Those wishing to attend are asked to notify the secretary, Cambridge University Medical School, The Naval Hut, Downing College, Cambridge, immediately.

British Association of Allergists.—The annual general meeting of the British Association of Allergists will be held at the Royal Society of Medicine, 1, Wimpole Street, London, W.1, at 11 a.m. on January 24. Speakers will include Dr. N. C. Oswald, Professor J. Gough, Dr. H. O. Schild, Dr. MacKenna, and Dr. I. B. Sneddon.

Congress of Universities.—The Seventh Quinquennial Congress of Universities of the British Commonwealth will be held at Cambridge in July.

NEW ISSUES

British Journal of Venereal Diseases.—The next issue (Vol. 28, No. 4) will be available in a week's time. The contents include:

CHANGING CONCEPTS IN THE SERO-DIAGNOSIS OF SYPHILIS: SPECIFIC TREPONEMAL ANTIBODY VERSUS WASSERMANN REAGIN. R. A. Nelson, Jr.

CARDIOLIPIN-ANTIGEN. II: A QUANTITATIVE EXAMINATION OF SENSITIVITY. Henning Schmidt. STATISTICAL APPENDIX by Michael Weis Bentzon.

PLURALITY OF ANTIBODIES IN SYPHILITIC SERUM AND CLINICAL PRACTICE. Vittorio Puccinelli.

RESULTS OF TREATMENT OF GONORRHOEA WITH PENICILLIN ALONE AND WITH PENICILLIN AND SULPHONAMIDE. G. O. Horne, J. B. Bittiner, and J. R. G. Buchanan.

THE INCIDENCE AND DEMONSTRATION OF BIOLOGIC REACTIONS IN ROUTINE WASSERMANN TESTS. H. M. Rice.

MANAGEMENT OF VESICAL DYSFUNCTION OF NEUROSYPHILIS BY TRANSURETHRAL RESECTION OF THE VESICAL NECK. W. Fowler.

HERPETIC URETHRITIS. Juvenal Esteves and Manuel R. Pinto.

ACUTE GONORRHOEA DUE TO A STREPTOMYCIN-RESISTANT GONOCOCCUS. W. J. Ryan.

ACETARSOL PESSARY DERMATITIS. J. O. Doyle.

Issued quarterly; annual subscription £2 2s., single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Journal of Industrial Medicine.—The next issue (Vol. 10, No. 1) will be available in a week's time. The contents include:

THE INFLUENCE OF HORMONES ON THE DEVELOPMENT OF SILICOTIC NODULES PRODUCED BY INTRAPERITONEAL INJECTION OF QUARTZ. Erich Schiller.

THE ACTION OF DIFFERENT FORMS OF PURE SILICA ON THE LUNGS OF RATS. E. J. King, G. P. Mohanty, C. V. Harrison, and G. Nagelschmidt.

SOME PSYCHOLOGICAL CONFLICTS CAUSED BY GROUP BONUS METHODS OF PAYMENT. Norah M. Davis.

EMOTIONAL STABILITY IN COLLIERY WORKERS. Alastair Heron and Dorothy Braithwaite.

AN INVESTIGATION INTO THE REMOVAL OF RADIOACTIVE CONTAMINATION FROM THE HANDS. James Gregory.

A FIELD STUDY OF OCCUPATIONAL DEAFNESS. Colin M. Johnston.

AGE AND INDUSTRIAL ACCIDENT RATES. H. F. King and D. Speakman.

Issued quarterly; annual subscription £2 2s., single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

Details in this column are necessarily brief. Further information and tickets where required (marked ●) should be obtained from the institution concerned.

Monday, January 19

HUNTERIAN SOCIETY.—At Mansion House, 8.30 p.m., Hunterian Society Lecture by Dr. J. Van Loer (Holland): Auto Mutilation of Prisoners.

ROYAL EYE HOSPITAL.—5 p.m., Dr. T. H. Whittington: Refraction Work in the Young and the Old. Aphakia.

Tuesday, January 20

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. A. S. Parkes, F.R.S.: Preservation of Living Cells at Low Temperatures.

CAERNARVONSHIRE AND ANGLESEY PAEDIATRIC CLUB.—At Clinic, Sackville Road, Bangor, 4.30 p.m., Dr. E. G. G. Roberts: Paediatric Radiology.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Professor P. B. Medawar: Pigmentation.

LONDON UNIVERSITY.—6 p.m., Sir Godfrey Thomson, D.Sc., Ph.D.: Geometry of Mental Measurement.

SOCIETY FOR THE STUDY OF ADDICTION.—At 11, Chandos Street, W., 8 p.m., Detective-Sergeant G. Lyle: Dangerous-Drugs Traffic in London. Discussion will follow.

SOUTH WEST LONDON MEDICAL SOCIETY.—8.30 p.m., Dr. Kenneth Cameron: Common Psychiatric Problems in Childhood.

WEST END HOSPITAL FOR NERVOUS DISEASES.—5.30 p.m., Mr. J. Minton: Ocular Manifestations in Nervous Disease: Part I.

Wednesday, January 21

EUGENICS SOCIETY.—At Burlington House, W., 5.30 p.m., Dr. J. D. Nisbet, Ph.D.: Family Environment and Intelligence.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Inflammation.

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, 4.30 p.m., Mr. J. E. Semple: Differential Diagnosis of Renal Pain.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital School of Medicine, 8.30 p.m., Sir William MacArthur: History of Smallpox in the British Isles.

LONDON UNIVERSITY.—6 p.m., Sir Godfrey Thomson, D.Sc., Ph.D.: Geometry of Mental Measurement.

MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 8.15 p.m., Dr. A. L. P. Peeney, Dr. A. M. Nussey, Dr. W. C. Smallwood, and Mr. C. Rudd: A Symposium on Cortisone and A.C.T.H.

Thursday, January 22

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Mr. H. J. Seddon: Certain Aspects of Nerve Repair.

●INSTITUTE OF CHILD HEALTH.—5 p.m., Dr. J. G. Scadding: The Chronic Cough.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Mycology—Pathogenesis of Tinea Capitis.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Dr. M. K. Alexander: Case of the Stevens-Johnson Syndrome; Dr. A. H. Cruickshank: Case of Chiari's Disease; Dr. K. McCarthy: Generalized Vaccinia.

LONDON UNIVERSITY.—6 p.m., Sir Godfrey Thomson, D.Sc., Ph.D.: Geometry of Mental Measurement.

OXFORD UNIVERSITY.—5 p.m., Dr. G. W. Corner (Washington): Medicine in the Poems of Chaucer.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Professor C. G. Rob: Intermittent Claudication and Gangrene of Toes by Arterial Grafting.

UNIVERSITY COLLEGE.—At Physiology Theatre, 5.30 p.m., Professor F. Bergel: Some Chemical Aspects of Normal Growth.

Friday, January 23

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. I. Muende: Anomalies of Pigmentation.

ROYAL EYE HOSPITAL.—5.30 p.m., Mr. Howard Reed: Visual Fields.

ROYAL INSTITUTE OF PHILOSOPHY.—At University Hall, 14, Gordon Square, W.C., 5.15 p.m., Mr. A. H. Smith, M.A.: Moral Philosophy in Ancient Greece.

ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., Symposium: Diabetes Mellitus.

ROYAL SANITARY INSTITUTE.—At Town Hall, Bournemouth, 10 a.m., Lord Douglas of Barloch: Soil, Food, and Health; Dr. K. O. A. Vickery: Keystones of Positive Health.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Barwise.—On December 29, 1952, at Frome St. Quinton, Dorchester, to Dr. Maureen (formerly Bassett), wife of Dr. David Barwise, a son—Michael David.

Fairley.—On December 20, 1952, at the R.A.F. Hospital, Rinteln, Germany, to Dorothy Jean (formerly Orr), wife of Dr. H. Barrie Fairley, M.B., B.S., D.A., a daughter.

Gray.—On January 1, 1953, at St. David's Hospital, Cardiff, to Marion (formerly Muir) and Dr. Peter Gray, a daughter.

DEATHS

Abbott.—On January 3, 1953, at 21, Vallance Gardens, Hove, Sussex, Horatio White Abbott, M.D., late of Holloway, London, N.

Carr.—On January 2, 1953, Jack Carr, M.R.C.S., L.R.C.P., of Manchester, Lancs.

Hughes.—On January 2, 1953, at 1, Seaforth Lodge, Barnes, London, S.W., John Hughes, M.B., B.Ch., D.P.H., aged 67.

Richards.—On January 1, 1953, at Brynhyfryd, Aberavon, Port Talbot, Glam., William Jones Richards, F.R.C.S., aged 79.

Ware.—On January 5, 1953, Arthur Maitland Ware, M.D., of Tyting Down, Guildford, Surrey, aged 78.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Regular Douching

Q.—*What are your views on the desirability of routine vaginal douching for reasons of personal cleanliness?*

A.—There is no need for the normal woman ever to use a douche for the purpose of keeping the vagina "clean." The vagina can very well look after itself in this respect, even to the extent of clearing itself of degenerating blood and endometrial debris within 24 hours of the end of menstruation.

Douching without a clear indication is not only unnatural and unnecessary but may well be harmful. The vagina and cervix depend for health on the particular environment provided by their secretions and by their bacterial inhabitants. Douching tends to wash these away and may modify the *p*H of the vagina, thereby encouraging vaginal infections and possibly erosion of the cervix.

Disinfection of Telephones

Q.—*In many industrial concerns it is the practice to "disinfect" the telephones once a week by wiping the mouthpiece of the instrument with a piece of paper impregnated with a disinfectant. It has been stated that the disinfectant action is retained over the week elapsing between treatments and that the procedure is of benefit in minimizing the spread of possible infection (e.g., influenza, etc.). Is there any reliable evidence for this?*

A.—So far as is known no convincing evidence has ever been produced that respiratory tract infections are spread by way of telephones, and a consideration of the mechanics of possible transmission does not suggest that such spread is very likely. One does not ordinarily touch the mouthpiece of the telephone when talking, so that transference by physical contact is improbable, and, since any microbes that are coughed into the mouthpiece are coated with saliva or sputum, they may be expected to adhere to the instrument when dry, and would be difficult to blow off by any jet of air from the mouth. It seems very unlikely that any tolerable antiseptic would long remain sufficiently active on the surface of the instrument to kill bacteria embedded in a protective coating. However, pathogenic bacteria can only very rarely be recovered from the mouthpieces of telephones even when they are not disinfected. At the same time the cleansing associated with "disinfection" may be useful from an aesthetic point of view.

Heat Spots

Q.—*What are "heat spots"? How are they best treated?*

A.—"Heat spots," or papular urticaria, is the usual pattern of urticaria seen in children between the ages of about 1 to 5 years. It differs from the adult pattern in that the lesion is not well demarcated and resembles a flea-bite. When the wheal and flare have subsided there remains a central papule, due to lymphocytic infiltration, which persists for seven to ten days. This papule is readily excoriated in an attempt to relieve itching. The condition is more frequently seen in the summer.

The causes of urticaria in childhood are similar to those of adult urticaria. Most cases relate to gastro-intestinal disturbance and are relieved by attention to diet, care of bowels, and the administration of alkalis. A proportion of the more persistent and intractable cases have an emotional basis and require treatment from this aspect. Specific food allergy, parasitic infestation, focal infection, constipation, carbohydrate excess, nervous instability, and emotional upsets are important causes.

It may be difficult to differentiate insect bites from papular urticaria, and the former may provoke the latter. The season and circumstances may help; an irregular rather than a symmetrical distribution and the presence of a puncture would suggest bites. Bites more readily become infected. In both affections lesions may be vesicular or bullous, especially on hands, feet, or lower legs, and more commonly in the very young and in hot weather. Infection may also be associated with blister formation.

Calciferol in Bazin's Disease

Q.—*Have large doses of calciferol been found to be of any use in Bazin's disease? The case I have in mind is that of a woman aged 40 who has had chronic ulceration of her lower leg for about six years. The ulcer, having formed, will not heal unless skin-grafted. The case has been classified as Bazin's disease at hospital, but tuberculosis has not been found on biopsy. The ulcers have failed to respond to any antibiotic given systemically.*

A.—Reports of the treatment of Bazin's disease with calciferol have not been very encouraging. The condition is, of course, rare in this country, particularly in a woman of this age. As tuberculosis was not found on biopsy the diagnosis should be called seriously into question, and if doubt still remains guinea-pig inoculation should be carried out. If the diagnosis of tuberculosis can be substantiated isoniazid is suggested as a treatment more likely to succeed.

Salty Taste in Mouth

Q.—*My patient complained first of a bad taste in the mouth; this was traced to tonsils, which have been removed. Ever since then she complains bitterly of a permanent salt taste, and I write to ask the cause of this. Her gums and teeth are beyond reproach.*

A.—A patient commonly complains of a salty taste in the mouth when there is bleeding from the gum margin or discharge into the mouth from parodontal disease or a chronic abscess or cyst. The first two of these causes are excluded if the statement that the teeth and gums are beyond reproach means that there has been a thorough clinical examination, including vitality tests of the teeth, and full mouth radiographs. A chronic abscess or cyst may discharge its contents into the mouth through a small sinus which is sometimes very difficult to find, but the lesion would show in a radiograph as a radiolucent area. In the case of a cyst the area would be limited by a white line.

In the absence of these causes, any interference with the mechanism of taste must be investigated, special attention being given to the lingual and glosso-pharyngeal nerves.

Bitter Taste in Mouth

Q.—*A woman of 47 has complained of a bitter acid taste in the mouth for 18 months. The condition is worse when dentures are worn. Dental examination reveals no abnormality, and acrylic dentures have been changed to vulcanite. The patient has not yet reached the menopause. Can you advise on the cause and treatment?*

A.—So little is known about this troublesome complaint that the implications in the question very nearly supply such answers as can be given.

A bitter, acid taste occurs most usually in women of middle life, and it seems that it is nearly always associated with the wearing of dentures. Dental experts suggest that the complaint is less common now that plastic dentures are

used more frequently than vulcanite ones. Biopsies have been taken of the gums without providing any solution to the problem, and extensive gingivectomies undertaken in the hope of eradicating hypothetical sepsis have proved unsuccessful. The age of the patients naturally suggests that the endocrine changes of the menopause may be causative, and oestrogens are invariably given a trial, but usually are without benefit. In the belief that the condition may be due to a vitamin deficiency, nicotinic acid and vitamin-B complex have been tried in almost every case, and allergy has been invoked as an explanation, but antihistamine drugs are without effect. The possibility that some heavy metal such as mercury is being excreted by the salivary glands should not be overlooked. Diabetics and those suffering from pernicious anaemia occasionally complain of this symptom, and when this is so specific treatment usually leads to their complete relief. Naturally a psychoneurosis has been invoked to explain most of the cases, and this may be so in some of them, but the truth is we know little about the condition and the treatment is empirical.

Post-mortem Removal of Eyes

Q.—*I should welcome advice on the post-mortem removal of eyes for later corneal grafting. (a) Am I right in believing that the consent of the executors is necessary, apart from the expressed wish of the deceased? (b) Is any eye with a healthy cornea suitable? (c) Must the eyes be removed within two hours of death to be of any use? (d) Into what solution should they be put? (e) To whom and where are the eyes to be sent? (f) Are there any special details of technique for this operation?*

A.—The answers to these questions are as follows:

(*a*) The consent of the executors is not necessary, but the eyes may not be removed if the surviving spouse or any surviving relative objects.

(*b*) The answer to this is yes, except where there is melanoma of the iris, glioma of the retina, or syphilis.

(*c*) Successful grafts have been obtained from eyes removed within 10 hours of death, but the sooner the eyes are removed the better the grafts are for optical purposes.

(*d*) The eyes should be placed in liquid paraffin in a sterile wide-mouthed stoppered jar, and kept in a refrigerator at 4° C.

(*e*) Eyes should be sent to the ophthalmic surgeon of the nearest centre at which corneal graft surgery is practised.

(*f*) There are no special details of technique in this operation except that the eyeball must not be opened. The standard technique of enucleation is used.

Treatment of Bed-wetting

Q.—*Is hypnosis useful in the treatment of bed-wetting?*

A.—Hypnosis, according to those who have practised it, is often useful in the treatment of bed-wetting. It is, of course, a symptomatic treatment, and should be applied only when the case has been investigated, an opinion reached about the causes of the bed-wetting, and a decision made that hypnosis is suitable.

Dyspeptic Constables and Others

Q.—*Can you give me any information on the incidence of peptic ulcers in policemen? A constable has advanced a claim that his ordinary duties have been a major factor in the development of a gastric ulcer, and I shall be glad of advice.*

A.—According to Ihre and Müller (*Acta med. scand.*, 1943, **116**, 33) the proportion of policemen among male ulcer patients in Stockholm is the same as the proportion among all other male patients with medical illnesses—in each case 1%. No special study of policemen was made in the recent investigation into occupational factors in the aetiology of gastric and duodenal ulcers undertaken in this country (*Spec. Rep. Ser. med. Res. Coun.* (*Lond.*), No. 276, 1951). The conclusion that "less variation of incidence has been found than might have been expected, if conditions of work played an important role in the genesis of the disease" may, however, be relevant. This is perhaps particularly so since the ulcer in the case referred to in the question is a gastric ulcer. Anxiety about work appeared to be unduly common in subjects with duodenal ulcer, but not in subjects with gastric ulcer. No evidence could be obtained that shift work or irregular meals played an important part in the causation of either type of ulcer. The most striking finding with regard to gastric ulcer was its greater prevalence among the poorer social classes and decreasing incidence as economic status improved. This would not, presumably, be considered evidence that the conditions of a policeman's life conduced to the development of gastric ulcers. A review of the literature on occupational factors in peptic ulcers is included in the M.R.C. publication.

NOTES AND COMMENTS

Corneal Herpes.—DR. C. HEATH and Dr. F. A. WHITLOCK (Truro) write: Your expert states that none of the new antibiotics has proved effective against the herpes group of infections ("Any Questions?" December 6, 1952, p. 1270). Surely it is recognized that the virus of herpes simplex is sensitive to aureomycin?[1 2 3] It is true that, once established beneath the corneal epithelium, the infection may prove inaccessible to surface applications, but in suitable cases it may be controlled. Recently a child of eight months gravely ill with Kaposi's varicelliform eruption—a condition usually regarded as the result of herpes simplex infection superimposed on an infantile eczema[4]—was found to have widespread dendritic ulceration of both corneas. After treatment with aureomycin by mouth and oculent. aureomycin. and atropin. to the eyes, the child made a complete recovery, the corneas healing without developing other forms of herpetic keratitis and without scarring. It seems most unlikely that this would have occurred without benefit of aureomycin.

REFERENCES

1 Baer, R. L., and Miller, O. B. (1949). *J. Invest. Derm.*, **13**, 5.
2 Bereston, E. S. (1949). Ibid., **13**, 13.
3 McConachie, J. A., and Anderson, T. E. (1951). *Brit. J. Derm.*, **63**, 307.
4 Ruchman, I., Dodd, K., and Welsh, A. L. (1947). *Arch. Derm. Syph.*, **56**, 846.

OUR EXPERT writes: There is no critical evidence that aureomycin has any effect on the herpes virus. This is borne out by an immense literature, and is generally accepted by virus experts, though it is true that there are a number of clinical reports to the contrary. Experimentally all that has been claimed for the newer antibiotics has been that they may have some prophylactic or inhibiting action on the virus. Experimental studies on the eye have led to essentially the same negative conclusion (Geller and Thygeson, *Amer. J. Ophthal.*, 1951, **34**, 165; Hallett *et al.*, *Arch. Ophthal. (Chicago)*, 1951, **46**, 33). The case reported by your correspondents is interesting, but, like all isolated case reports, is open to more than one interpretation. My own clinical experience with herpes infections of the eye treated with the newer antibiotics has been distinctly disappointing.

Correction.—In a paragraph headed "Methorphinan Scheduled" (January 3, p. 52) attention was drawn to an Order in Council relating to 3-methoxy-N-methylmorphinan. It was wrongly implied, however, that this substance was the same as methorphinan. Methorphinan is 3-hydroxy-N-methylmorphinan and it has been scheduled since July, 1951.

"Any Questions?" Book: Second Series.—This is now available, price 7s. 6d. (postage 6d. extra), from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

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